Recent advances in rhodium-catalysed conjugate addition reactions

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Recent Advances in Rhodium-Catalysed Conjugate Addition Reactions

Volume 1 of 1
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Abstract

The research presented herein is concerned with the exploration of rhodium-catalysed addition reactions with organoboranes encompassing the 1,4-addition enolate protonation to benzyl acrylate esters, and the synthesis of chiral organoboranes for use in the synthesis of natural products Hermitamides A and B.

Chapter 1 introduces the area of rhodium-catalysed conjugate addition as a tool for asymmetric synthesis. An extensive discussion of this methodology is included and recent advances in the area will be highlighted. In addition to this some recently published alternatives to organoboranes are outlined and their use in rhodium-catalysed chemistry documented.

Chapter 2 discusses the tandem process of rhodium-catalysed conjugate addition enolate protonation, a recently observed asymmetric development. By using a novel route to benzyl acrylic esters the synthesis of α,α′-dibenzyl esters is achieved in excellent yields and selectivity. This study highlights the fact that when dealing with 1,1-disubstituted activated alkenes it is more difficult to produce enantioselective results as the chirality is determined in the protonation step and not during insertion. Some insights into the mechanism are proposed based on the outcomes observed.

Chapter 3 describes the total synthesis of Lyngbic Acid and related structures Hermitamides A and B. Synthesis of these natural products are achieved by synthesis of an enantiopure organoborane species and its subsequent coupling *via* rhodium catalysis. Some interesting insights into the addition of alkenyl organoborane species to unsubstituted 1,1-activated alkenes are detailed.

Chapter 4 describes the synthesis and characterisation for the compounds discussed in the previous chapters.

Acknowledgments

First and foremost I would like to say a huge thank you to my supervisors Dr. Chris Frost and Mr. Robert Gleave. I have really enjoyed my time working for you both and the guidance you have given me over the last 3 years.

Special thanks go to Prof. Paul Raithby for X-ray structures; getting data out of small organic molecules is always a challenge.

I'd like to also thank all the members of the Frost Group past and present, especially Dr Steve Flower, Dr Jerome Le Notre, Dr Ludivine Zoute, Ben Hartley, Joseph Allen, Jimmy White and Hannah Edwards. I'd like to mention especially Dr Chris Chapman for all his honesty, support and rugby chat – "there's always next year". Also big thanks to Jon Hargrave, ever present lab buddy and all-round good guy, 8 years of good memories coming to an end.

Also all my housemates over the last 3 years, firstly at Entry Hill Villas – Nicola, Noddy and JB, and "Team" 31 Second Avenue – Kelly, Ewan & Phillip – always remember house fish, chips, Rio nights and Bomberman.

And last but by no means least Emma & Helen, for keeping my chin up when I needed some reassurance, a hot meal or cakes…

Table of Contents

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
anhyd	anhydrous
Anal.	analytical (spectrometry)
app.	apparent
aq	aqueous
Ar	aryl
BBN	9-borabicyclo-[3.3.1] nonane
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
bnd	bicyclo[3.3.1]nona-2,6-diene
bod	bicyclo[3.3.1]octa-2,6-diene
Boc	tert-butoxycarbonyl
br	broad (spectral)
BTF	benzotrifluoride
Bu	normal (primary) butyl
t-Bu	*tert*-butyl
Bz	benzoyl
ºC	degrees Celsius
calcd	calculated
cat.	catalytic quantity
CHIRAPOS	(−)-bis(diphenylphosphino)butane
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
coe	cyclooctene
δ	chemical shift in parts per million downfield from tetramethylsilane
COSY	correlation spectroscopy
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
d	day(s); doublet (spectral)
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
º	degrees (angle)
DDQ	dichlorodicyanoquinone
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DIFLUOR-PHOS	5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DIPPHEN	4,7-diphenyl-1,10-phenanthroline
DMAP	4-(N,N-dimethylamino)pyridine
DMF	dimethylformamide
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
DOLEFIN	5-Benzyl-8-methoxy-1,8-dimethyl-2-(2′-methylpropyl)-bicyclo[2.2.2]octa-2,5-diene
DPPB	1,1′-bis(diphenylphosphino)butane
DPPF	1,1'-bis(diphenylphosphino)ferrocene

DPPM	1,1'-bis(diphenylphosphino)methane
DUPHOS	1,2-Bis((2R,5R)-2,5-dimethylphospholano)benzene
EDA	ethylene diamine
EDC	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
e.e.	enantiomeric excess
EI	electron impact (in mass spectrometry)
Et	ethyl
eq.	equivalent(s)
EWG	electron withdrawing group
FAB	fast atom bombardment (in mass spectrometry)
g	gram(s)
GSK	Glaxo Smith Kline
h	hour(s)
HKR	hydrolytic kinetic resolution
HMDS	hexamethyldisilazide
HPLC	high-performance liquid chromatography
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectrometry)
JOSIPHOS	1-[(S)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
L	litre(s)
n	wavenumber(s)
L-Gla	γ-carboxy-L-glutamic acid
lit.	literature
m	micro
mW	microwave
m	milli; multiplet (spectral)
M	molar (moles per liter); mega
M^+	parent molecular ion (in mass spectrometry)
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	melting point
MS	mass spectrometry
MVK	methyl vinyl ketone
m/z	mass-to-charge ratio (in mass spectrometry)
nap	naphthalene
nbd	norbornadiene
NMR	nuclear magnetic resonance
NORPHOS	2,3-Bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
PCC	pyridinium chlorochromate
Ph	phenyl
Phe	phenylalanine
PMB	para methoxybenzyl
ppm	part(s) per million
Pr	propyl
i-Pr	iso-propyl
Py	pyridine
q	quartet (spectral)

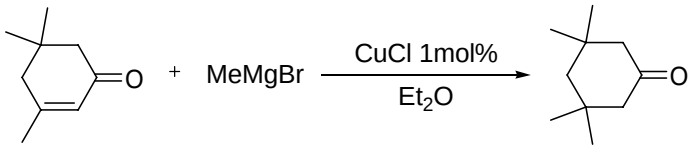
QUINAP	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
qu	quintet (spectral)
rac	racemic, racemate
R_f	retention factor (in chromatography)
RCM	ring closing methesis
rt	room temperature
s	singlet (spectral)
Sep	septet (spectral)
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	tributylsilyl
TFA	trifluoroacetic acid
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TMSOTf	trimethylsilyltriflate
TON	turnover number
tol	tolyl
t_R	retention time (in chromatography)
xyl	xylyl

Chapter 1 - Introduction

1.1 Overview

The ability to form a carbon-carbon bond is a fundamental desire of all synthetic chemists. Reactions of this type have been known since 1845 when Kolbe described the synthesis of acetic acid from inorganic precursors.[1] More recently the use of Diels-Alder,[2] Wittig reactions[3, 4] and palladium-catalysis[5] has proved to be robust and reliable methods of carbon bond formation. Celebrated reactions such as the Kumada-Corriu,[6-8] Mirozoki-Heck,[9] Stille,[10] Sonogashira,[11, 12] Negishi[13] and Suzuki-Miyaura[14] couplings permit the use of a range of organometallic reagents with numerous substrates leading to applications in medicinal and natural product synthesis.

The conjugate-additions to enones has been known since 1900 when Kharasch successfully reacted isophorone (**1.1**) with methyl magnesium bromide (**1.2**) in the presence of a catalytic quantity of copper chloride to give 3,3,5,5-tetramethylcyclohexanone (**1.3**) (*Scheme 1*).[15]



1.1 **1.2** **1.3**

93% yield

Scheme 1

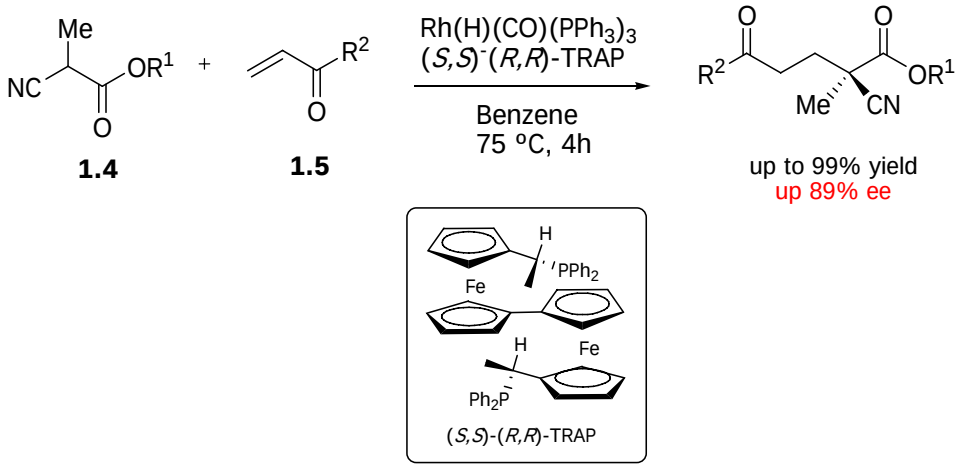
Since then a vast number of studies on metal-catalysed reactions with organometallic reagents such as Grignard and organolithium species have been published.[16] Using metal complexes such as copper, nickel and palladium complexes 1,4-addition can be undertaken with excellent selectivity.[17-19] The problem with many of these reagents is their inherent instability to air and moisture leading to difficulty in handling and manipulation of reactions.

One solution is the use of rhodium-catalysed conjugate addition reactions, with organometallic reagents such as boronic acids. Such reactions are complementary to previously studied methodology and give good functional group tolerance in addition to being air and water

stable.[20] The reaction has evolved significantly since early reports, and is becoming a more widely used process in a synthetic chemist's toolbox.[21]

1.2 Rhodium-Catalysed Conjugate Addition Reactions

The first highly enantioselective conjugate addition utilising rhodium catalysis was described by the group of Ito in 1991,[22] with the seminal conjugate addition of α-cyano carboxylates (**1.4**) to a range of vinyl ketones (**1.5**) or acrolein (R^2 = H). Using these activated nitrile nucleophiles allows the formation of products with all-carbon quaternary centres in excellent yields and selectivity (*Scheme 2*).



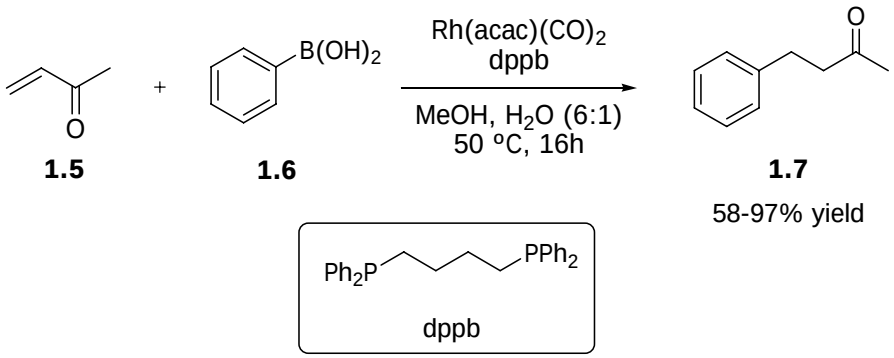
Scheme 2

This early work shows some of the preferential features of rhodium catalysis. The reaction occurs at moderate temperatures, with a low loading of catalyst (0.01-1 mol %) and good atom economy (1:1.5 equivalents substrate to nucleophile). Most importantly the reaction gives near-enantiopure products and quantitative yields. Such catalytic metal-enantiopure ligand systems are seen as some of the most elegant methods for carbon-carbon bond forming reactions. For the rest of this review work will concentrate on the area of rhodium-catalysed conjugate additions of organoboranes and boronate systems with discussion of major developments.

1.2.1 Boronic Acid Additions to Enones

The first published rhodium-catalysed conjugate addition of aryl and alkenyl boronic acids to methyl vinyl ketone (MVK) (**1.5**) was described by Miyaura and co-workers in 1997.[23] It

was found that using phenyl boronic acid (**1.6**) and a catalytic amount of a neutral rhodium precursor [Rh(acac)$(CO)_2$] with an achiral bidentate phosphine ligand such as diphenylphosphinobutane (dppb) in a range of solvents (methanol, DMF, cyclohexane) at 50 ºC, the desired Michael adduct 4-phenylbutan-2-one (**1.7**) was obtained in moderate to good yields (*Scheme 3*).

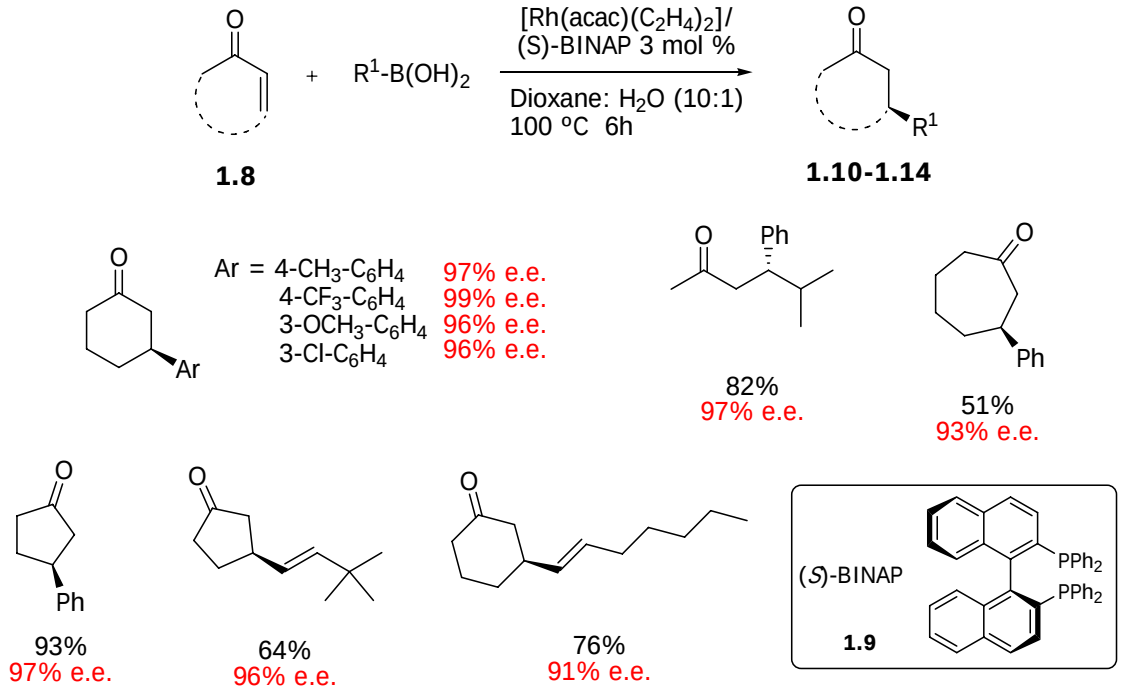


Scheme 3

A range of achiral ligands, solvents and temperatures were screened, with the bite angle of the phosphine ligand being critical to conversion to product. Ligands with a large P-Rh-P bite angle gave higher conversions in the order of dppb> dppp> dppe. Monodentate ligands such as $AsPh_3$ and PPh_3 were less effective in the reaction giving lower yields. This effect becomes more pronounced with a less activated substrate such as 2-octen-4-one with low conversions observed along with a number of rhodium-ligand permutations, which contrasts with methyl vinyl ketone. Numerous electron donating and withdrawing aryl boronic acids can be utilised in the addition with no loss in product yield. Sterically bulky *ortho*-substituted aryl groups can also be incorporated successfully by increasing the quantity of boronic acid to 2 equivalents to achieve a significant yield.

The first enantioselective rhodium-catalysed 1,4-addition was observed in collaboration by Hayashi and Miyaura.[24] Addition of aryl and alkenyl boronic acids to 2-cyclohexenone (**1.8**) proved inadequate with [Rh(acac)$(CO)_2$] as the rhodium source. Upon changing the metal precursor to [Rh(acac)$(C_2H_4)_2$] with (*S*)-BINAP (**1.9**) as the chiral phosphine ligand, heating to 100 ºC gave the desired 3-substituted cyclohexanone (**1.10-1.14**) in high yields and selectivity. NMR studies observed the formation of a single catalytic species based on rhodium-BINAP combination in deutero-benzene, with analogous [Rh(acac)$(CO)_2$] experiments showing a

number of species based on ^{31}P NMR.[24] The reaction is tolerant to both cyclic and acyclic enones, as well as electron rich and poor organoboronic acids, giving a wide range of products with high selectivity (*Scheme 4*).

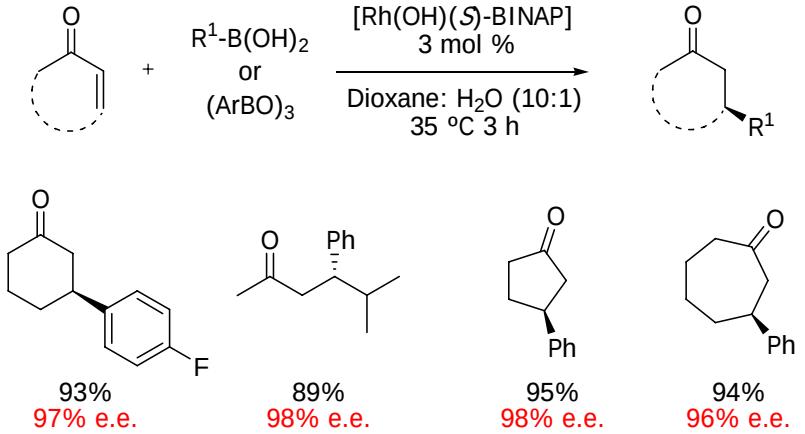


Scheme 4

This reaction has proved to be the benchmark for rhodium-catalysed conjugate addition chemistry. The reaction is tolerant to a wide range of functionality on both the organoboronic acid group and the enone. Both linear and cyclic enones can be utilised successfully and multigram scale reactions have been undertaken with high catalyst turnover and no loss of enantioselectivity.[25] Since then the procedure has been constantly refined with a range of rhodium sources, chiral ligands and bases being added to improve reaction times, enantioselectivity and catalyst loading.[26, 27]

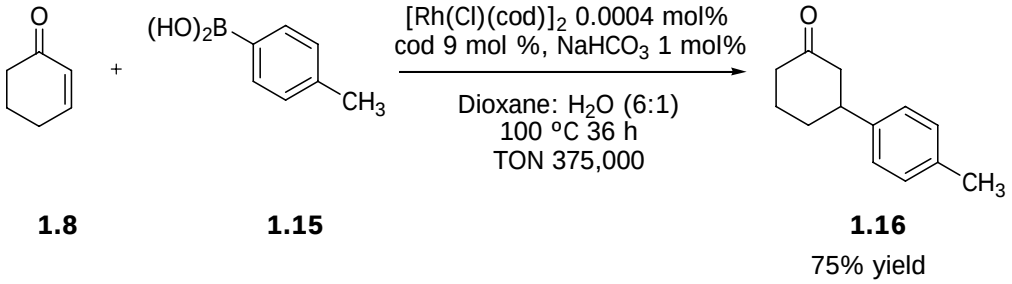
A number of rhodium sources are now utilised in rhodium-catalysed conjugate additions. Up until recently $[Rh(acac)(C_2H_4)_2]$ has been widely utilised in such reactions with good success, however, this has been generally superseded by $[Rh(Cl)(C_2H_4)_2]_2$ due to its superior ability to form chiral complexes *via* loss of ethene gas. Other rhodium complexes of interest are the cationic $[Rh(cod)_2][PF_6]$,[28] $[Rh(nbd)_2][BF]_4$,[29] and neutral $[Rh(cod)OH]_2$,[30] and [Rh(*S*-BINAP)OH]$_2$.[31]

Rhodium hydroxyl complexes have led to significant improvement in reaction times and lower temperatures.[31, 32] The group of Maddaford and co-workers had previously observed that the addition of an aqueous base provides a great acceleration effect on the reaction with the time taken reduced from 6 hours to 15 minutes.[33] Hayashi mirrored these findings determining that using a rhodium precursor without the acetylacetonate (acac) ligand should prove a superior catalyst for conjugate-addition of organoboronates.[31] The group found that [Rh(*S*-BINAP)OH]$_2$ was a highly active catalyst for a range of enones. Utilising organoboronic acids or organoboroxime species it was possible to lower the operating temperature of reaction without any loss in catalytic activity (*Scheme 5*).



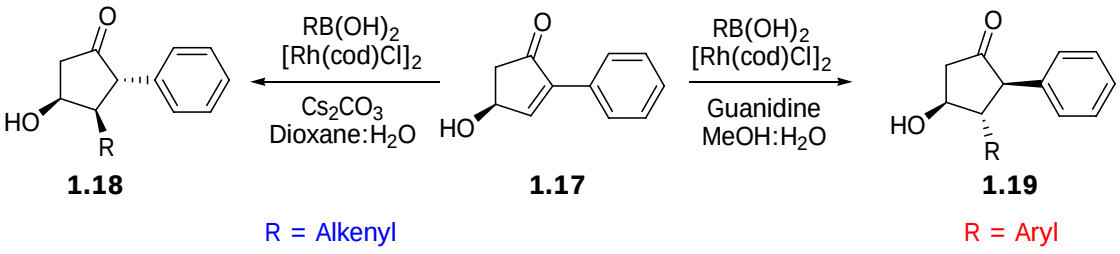
Scheme 5

Combining the findings in these publications led to the ability to use rhodium-catalysed conjugation addition reactions in large scale processes.[25] Itooka *et al.* have shown that the use of an aqueous base such as sodium hydroxide, sodium bicarbonate or potassium phosphate allows the addition of *p*-tolyl boronic acid (**1.15**) to cyclohexenone (**1.8**) at 0- 5 ºC with complete conversion to 3-*p*-tolylcyclohexanone (**1.16**).[30] The group found that ligands based on an olefin backbone such as 1,5-cyclooctadiene (cod) or norbornadiene (nbd) gave improved turnover over phosphine based ligands. Through this discovery catalyst loading could be successfully lowered and using elevated temperatures high catalyst turnover numbers (TON) could be achieved (*Scheme 6*).



Scheme 6

Using a higher loading of complex (3 mol%) with olefin based ligands such as cod or cyclooctene (coe) allows conjugate-addition reactions to occur readily at room temperature. Csaky has observed the stereoselective Rh(I)-catalysed conjugate addition reaction of aryl and alkenylboronic acids to unprotected 2-phenyl-4-hydroxycyclopentenone (**1.17**).[34] The free hydroxy group on the substrate is of high importance for the stereochemical outcome of the reaction. For aryl boronic acid additions only the *cis* isomer (**1.18**) is formed upon reaction with 2-phenyl-4-hydroxycyclopentenone. This is explained by the coordination of rhodium-aryl species to the alkene bond of the substrate taking place on either diastereotopic face of the unsaturated ketone. However, chelation with the OH group stabilises the formation of the *syn*-complex. Steric factors account for the *cis* geometry in this case. Modification of the base for alkenyl boronic acids leads to single stereoisomers of the 2-phenyl-4-hydroxycyclo-pentanones, inorganic bases such as LiOH lead to high *trans* selectivity (**1.19**), whereas using a bulky organic base such as guanidine gives *cis* products. Such compounds show the mild nature of conjugate-addition and could prove invaluable in the synthesis of novel prostaglandin derivatives (*Scheme 7*).



Scheme 7

1.2.2 Evolution of Chiral Ligands

There are numerous ligands utilised for rhodium-catalysed conjugate additions. Olefin type ligands such as cod and nbd have shown excellent results in conjugate-addition catalysis. Other systems include a range of both monodentate and bidentate achiral phosphine ligands such as dppm, dppb and dppf which have been utilised in conjunction with cyclic enones with good results.[27, 35] Water soluble phosphines have also shown promise in rhodium and palladium catalysed chemistry. The contribution of Shaughnessy (**1.20**),[36, 37] Lautens (**1.21**),[38] Genet (**1.22**)[39, 40] and others,[41, 42] allow carbon-carbon bond forming reactions to be undertaken in aqueous media (*Figure 1*).

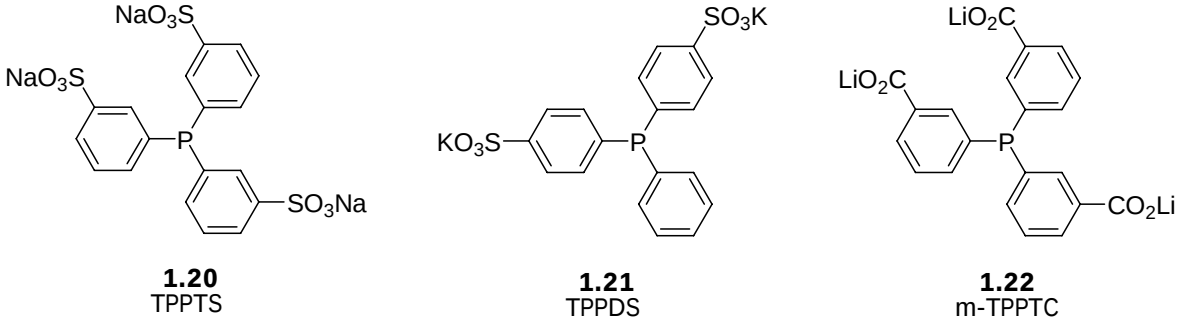


Figure 1

For asymmetric processes, atropisomeric ligands such as BINAP and its derivatives have been highly successful in 1,4-addition reactions. In addition to this, an extensive range of ligands have also been employed with varying success in the addition of aryl boronic acids to cyclohexenone including organocatalysis[43] and *N*-heterocyclic carbenes.[44]

Chelating bisphosphine ligands based on a chiral 1,1'-bi-2-naphthol (BINOL) backbone such as *digm*-BINAP (**1.23**) give both excellent yields and enantioselectivity (*Figure 2*).[39] The basic structure contains two guanidinium salts and was designed for aqueous conjugate-addition reactions. Unfortunately this catalyst system fails when water is used as the only solvent; however addition occurs in ethylene glycol in the presence of a base with high efficiency. Genet has also pioneered electronic tuning in atropisomeric diphosphanes with the DIFLUORPHOS ligand (**1.24**).[45] By incorporating the bi(difluorobenzodioxole) motif into the backbone of the structure, a narrow dihedral angle combined with an unusual π-acidity compared other biphenyl-based ligands was observed. P-PHOS (**1.25**) is a phosphine ligands encompassing 2,6-dimethoxypyridyl groups, with *ortho* groups which block the access of the

pyridyl nitrogen atoms to the metal centre have also proved valuable ligands for asymmetric synthesis.[46] Formation of a [Rh(acac)((*S*)-P-PHOS)] complex, generated *in situ* from equimolar of [Rh(acac)(C_2H_4)$_2$] and (*S*)-P-PHOS in aqueous dioxane system at 100 °C has also been found to be well-suited for rhodium-catalysed transformations.[47]

Reetz[48] and Miyaura[29] have both proposed 1,1′-binaphthol-based diphosphonites (**1.26, 1.27**) as ligands for rhodium-catalysed conjugate additions. The ligands are readily synthesised and require no chiral HPLC or resolution to give enantiopure compounds. Much optimisation is required for these systems as the ligands are strongly dependent not just on the choice of (*R*)- or (*S*)-BINOL but also on the achiral backbone for their selectivity. Although this phenomenon cannot be completely understood, it can be related to the increased flexibility of the backbone of the Rh-complex in conjunction with rhodium-phosphorus bite angles.

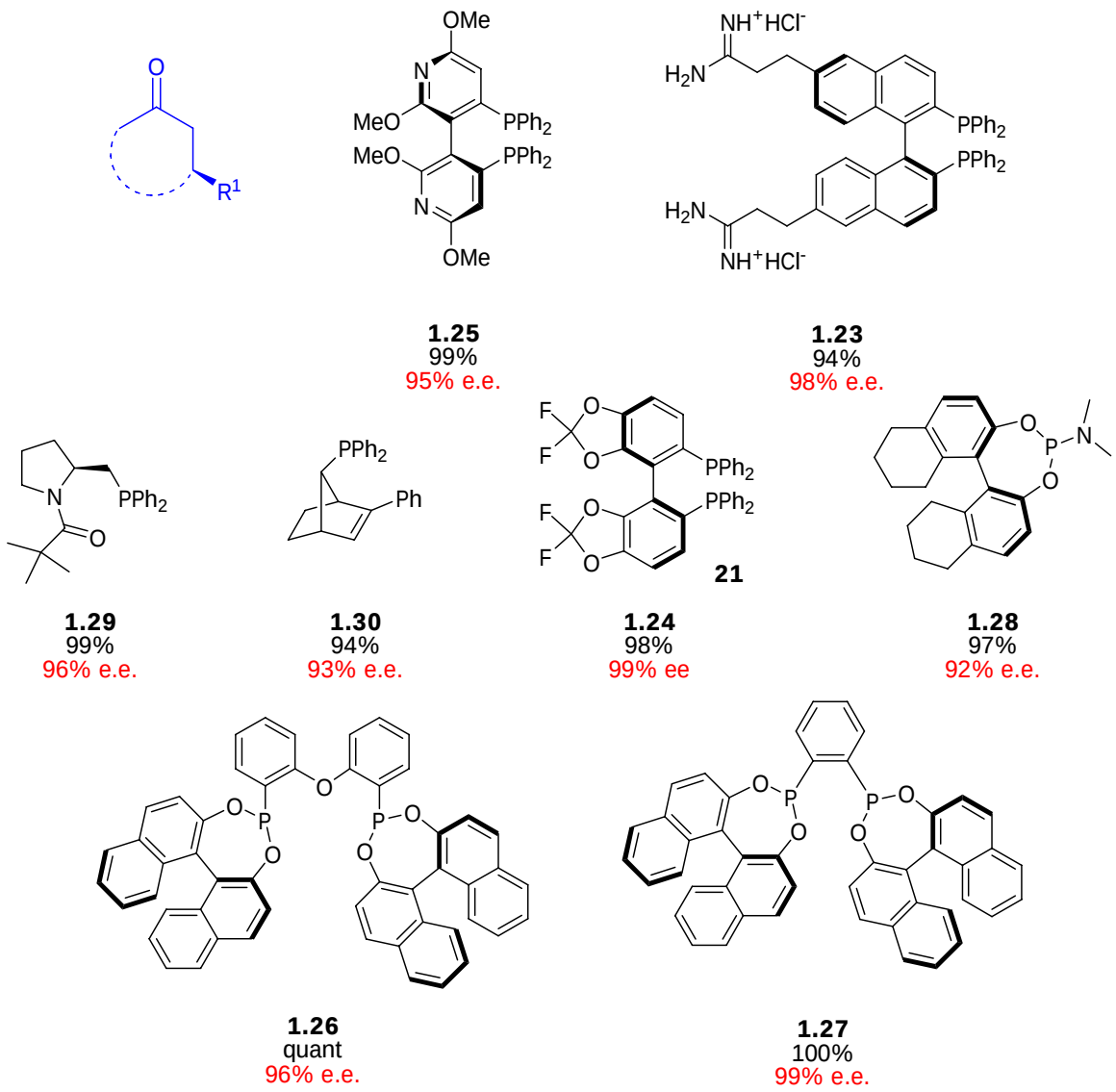


Figure 2

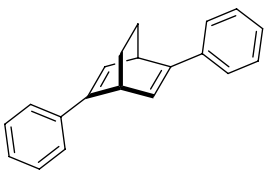
Monodentate phosphoramidites such as H_8-MonoPhos (**1.28**) pioneered by Feringa and co-workers have proved to be excellent ligands for conjugate-additions.[49-51] One of the major advantages of such ligands is their ease of preparation and structural flexibility. By varying the amine a library of asymmetric ligands can be rapidly and inexpensively assembled. This can be combined with combinatorial techniques to rapidly screen a reaction for the optimum conditions.[52]

Tomioka and co-workers have described amidomonophosphine (**1.29**), a ligand derived from L-proline, that contains a carbonyl oxygen atom as the hard donor site in addition to the soft

phosphorus atom donor forming a hemi-labile system.[53] Although excellent results are observed, it is important to note that the system is highly sensitive to ligand-metal ratio and cationic rhodium sources give no yield or asymmetric induction. A range of analogues were prepared with modifications to the proline backbone, however, none were as successful as the original ligand. Another hemi-labile system is the chelating alkene-phosphine ligand such as the norbornadiene based ligand (**1.30**) synthesised by Duan *et al.*[54] Such ligands should combine the advantages of both phosphine and diene type ligands, giving good rigidity and metal phosphine coordination, along with the ideal chiral environment around the rhodium centre. These ligands give selectivity similar to chiral bisphosphines with excellent yields. Comparing reaction kinetics of a (**1.30**)-Rh complex in the 1,4-addition reaction to methyl vinyl ketone takes only 3 minutes for 50% conversion to product in comparison to 16h for phosphine only ligands. This result shows that the catalyst activity of (**1.30**)-Rh species is closer to a rhodium-cod complex rather than Rh-BINAP. The group therefore suggests that the olefin portion of ligand is mainly responsible for determining its catalyst activity and not the phosphine moiety.

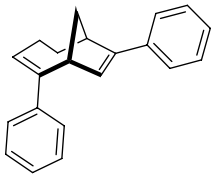
The final major class of metal complexes for asymmetric conjugate addition are the chiral diene-rhodium complexes. Such systems can be readily substituted for chiral phosphines in enantioselective processes, but have also proved effective in reactions where phosphine ligands fail.[55, 56] A range of chiral diene ligands have been synthesised by Hayashi (**1.31-1.34**),[57-59] Carreira (**1.35-1.37**),[60] Grützmacher (**1.38**),[61] and others,[62, 63] give a number of low weight, air stable organic compounds which readily coordinate to late-transition metals (*Figure 3*).

Hayashi:

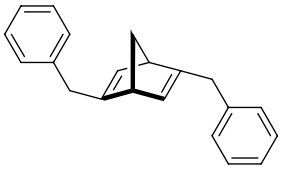


1.31
(*R,R*)-Ph-bod*

1.32
(*R,R*)-Bn-bod*

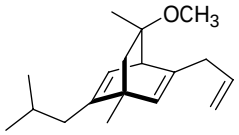


1.33
(*R,R*)-Ph-bnd*

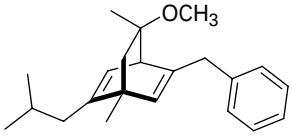


1.34
(*R,R*)-Bn-nbd*

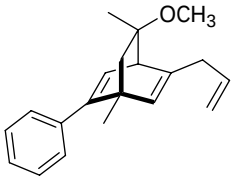
Carreira:



1.35
(*R,R,R*)-Dolefin

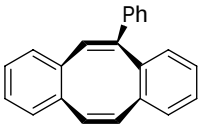


1.36



1.37

Grützmacher:

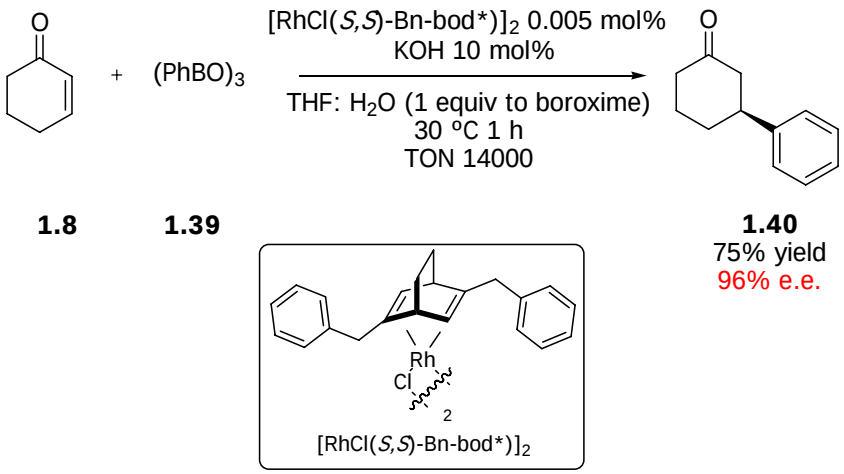


1.38
Ph-dbcot

Figure 3

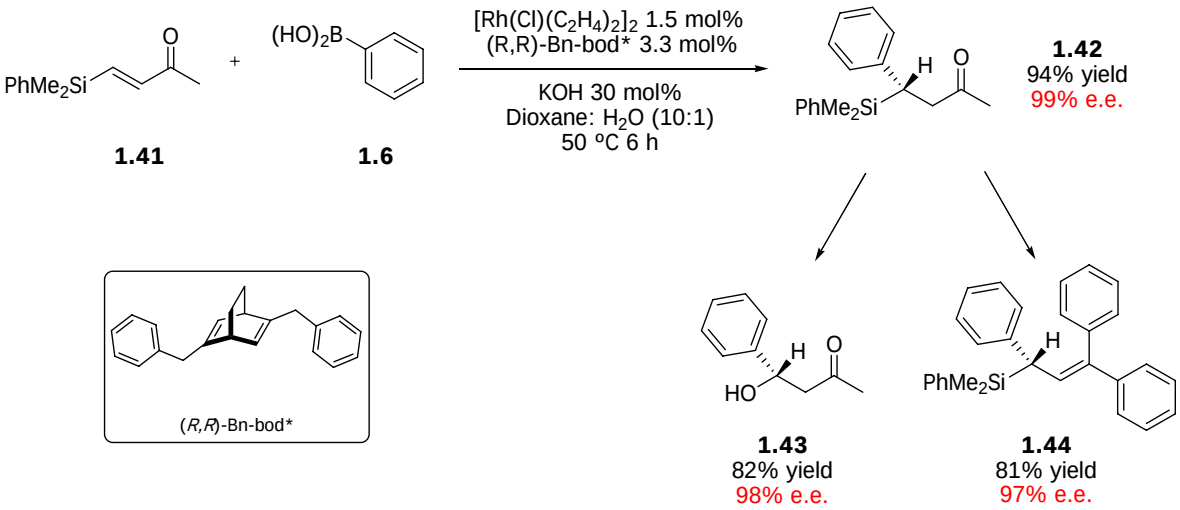
These rhodium-ligand systems have afforded high stereocontrol in a range of complex product synthesis. Hayashi and co-workers have utilsised chiral-diene based catalysis in the additions to enones,[55, 64] esters,[65, 66] α,β-unsaturated aldehydes,[67] α,β-unsaturated Weinreb amides[68] and substituted maleimides.[69] In addition to this 1,2-additions to protected aryl imines[70] and aldehydes[71] and tandem arylation alkyne-alkene cyclisations[71] can be undertaken with excellent results.

To illustrate the potential of chiral diene catalysis especially in rhodium-catalyzed aryl transfer reactions Hayashi has demonstrated the exceptional turnover of the catalyst system to cyclohexenone (**1.8**).[55] Using the preformed [RhCl(*S,S*)-Bn-bod*)]$_2$ catalyst system a range of enones could be successfully arylated in high selectivity at room temperature with a 0.05 mol% catalyst loading. Interestingly the use of boronic acids resulted in a low yield of the product, with 3 and 5 equivalents of boronic acid giving the product in 37% and 0% yield, respectively. To this end phenylboroxine (**1.39**) which was prepared from phenyl boronic acid by azeotropic removal of water and subsequent washing with hexane gave superior yields of 3-phenylcyclohexanone (**1.40**) even at 0.005 mol% catalyst. Phosphine ligands were all unsuccessful at such low loadings showing the superior reactivity of chiral diene systems (*Scheme 8*).



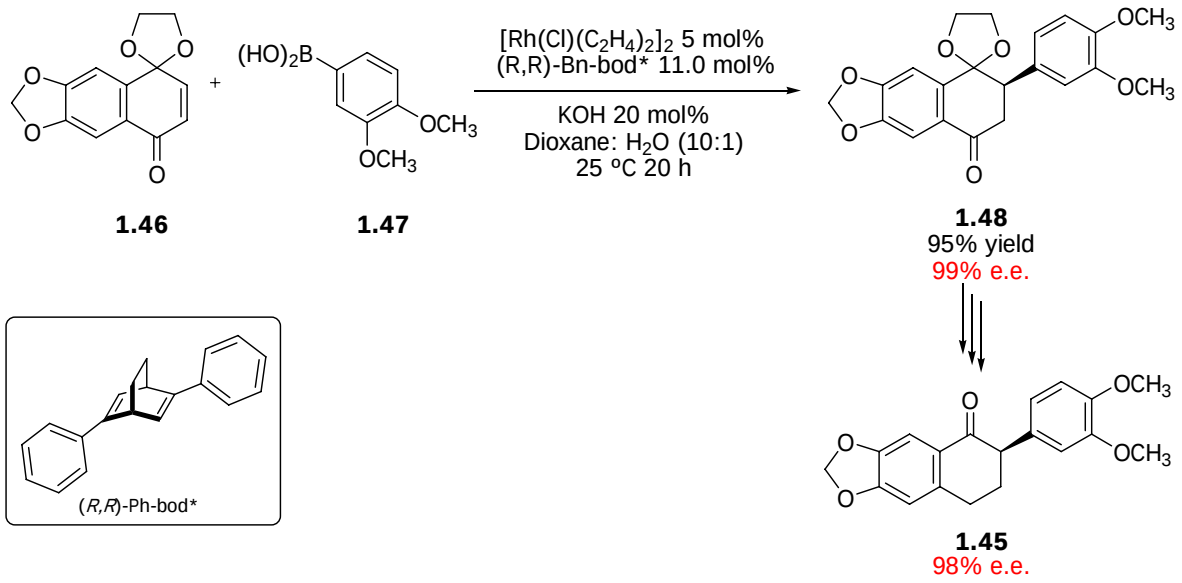
Scheme 8

Chiral diene catalysis can be utilised in the asymmetric 1,4-addition of arylboronic acids to β-silyl α,β-unsaturated carbonyl compounds (**1.41**), providing a novel method for the construction of chiral organosilicon compounds.[72] The reaction occurs under mild conditions with only 1.5 equivalents of phenyl boronic acid being utilised to complete the transformation, it is also noted that other phosphine ligands such as BINAP or phosphoramidites give markedly lower enantioselectivity. The newly formed enantio-enriched chiral 4-(dimethyl(phenyl)silyl)-4-phenylbutan-2-one compounds (**1.42**) can be manipulated to give the corresponding β-hydroxyketones (**1.43**) or allylsilanes (**1.44**) with minimal loss in enantioselectivty (*Scheme 9*).



Scheme 8

1,4-addition reactions can also be used to mediate a pseudo-α arylation procedure leading to a novel synthetic approach to 2-aryltetralones utilising naphthoquinone monoketals as substrates.[64] These products are highly desirable as biological compounds and a catalytic route using rhodium catalysis rather than using previously described stoichiometric chiral reagents. The α-substituted chiral ketone product (**1.45**) is an important intermediate in the synthesis of hexahydrobenzo[c] benzophenanthridine alkaloids.[73] Although higher catalyst loading is required compared to previous enone additions, the reaction still tolerates the bulky ethylene ketal moiety in close proximity to the reacting β-position of the enone (**1.46**). The reaction proceeds at room temperature with 3,4-dimethoxyphenylboronic acid (**1.47**) and acetal protected product (**1.48**) is formed with high enantoselectivity. Key intermediate (**1.45**) can be furnished in 4 steps *via* standard chemical reactions (*Scheme 10*).

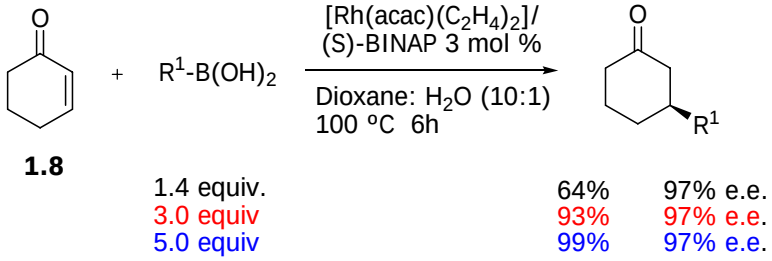


Scheme 9

1.2.3 Range of Boron Reagents

The remaining limitation of rhodium-catalysed conjugate addition reactions is the quantities of boronic acid required for significant quantities of product to be formed. This is due in part to the competing pathway of rhodium-catalysed reduction of the boronic acid producing the aromatic compound or homo-coupling in the case of more reactive organometallic species. Returning to the rhodium-catalysed addition of boronic acids to cyclohexenone (**1.8**) it is

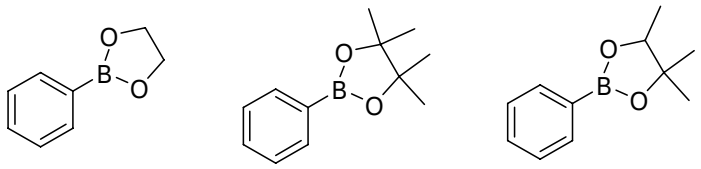
observed that only with 5 equivalents of boronic acid does the reaction give full conversion to product (*Scheme 11*).



Scheme 11

Boronic acids are often the coupling partners of choice for conjugate-addition reactions, over 450 examples are commercially available, however, many are not simple to purify and manipulate due to their physical properties. Excesses of material also have to be used as concentration of boronic acid is complicated by competing equilibrium of trimeric cyclic anhydrides (boroxines) in solution, leading to reaction mixtures that are difficult to accurately measure stoichiometrically. Consequently more complex boronic acids are infrequently used in conjugate-addition chemistry due to the inefficient use of the most precious and often costly component in the reaction.

Viable alternatives are ethylene glycol (**1.49**), pinacol (**1.50**) and 2-methyl-2,4-pentanediol (**1.51**) based boronate esters, which are readily utilised in palladium-catalysed couplings.[14] These boronic esters exist as monomeric complexes with defined structures, thereby aiding precise adjustment of stoichiometry (*Figure 4*).

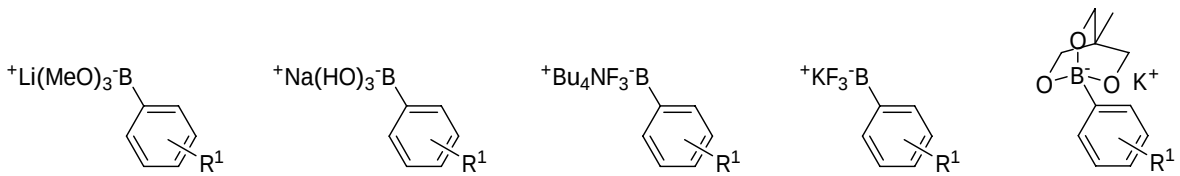


1.49 **1.50** **1.51**

Figure 4

However, the compounds are often commercially expensive and not as atom efficient as boronic acids. Also they are generally ineffective in conjugate-addition reactions with only a small number of examples reported. [74, 75]

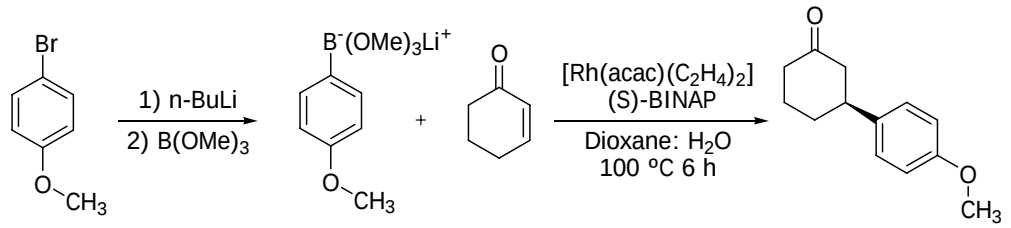
One solution is the use of boronate reagents to mediate transmetallation as such reagents can be readily prepared *in situ*, isolated and in general stored indefinitely in the presence of both air and water. A number of boronate esters with a variety of counterions have been formed with uses in organometallic reactions (**1.52-1.56**) (*Figure 5*).[76]



1.52 Hayashi | **1.53** Cammidge | **1.54** Batey | **1.55** Vedjes | **1.56** Miyaura

Figure 5

The first examples of boronate esters being used in rhodium-catalysed transformations was described by Hayashi utilising *in situ* lithiation of aryl bromides (**1.57**) followed by treatment with trimethoxyborane to yield lithium trimethoxyboronate species (**1.52**).[77] Such reagents were then used in the conjugate-addition of the 4-methoxy phenyl group to cyclohexenone (**1.8**), a reaction which did not occur by conventional boronic acid coupling. The reaction is highly sensitive to the amount of water present, with extremes of water concentration limiting the formation of 3-(4-methoxyphenyl)cyclohexanone (**1.58**), by acceleration of aryl-boron bond hydrolysis. Only when the balance of water to boronate ester is adjusted to 1 equivalent, good yields and enantioselectivity are observed, even at rhodium loadings of 0.1 mol%. The problem with such reagents is their lack of inherent stability, the materials must be synthesised daily and without exposure to water. Upon standing in air mixtures of inactive species such Li[PhB(OMe)$_2$(OH)] and PhB(OMe)(OLi) form with residual methanol (*Scheme 12*).

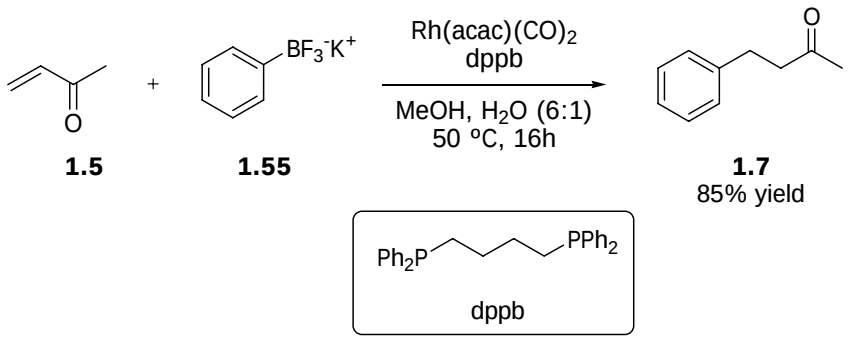


1.57 | **1.52** | **1.8** | **1.58** 86% Yield 98% e.e.

Scheme 12

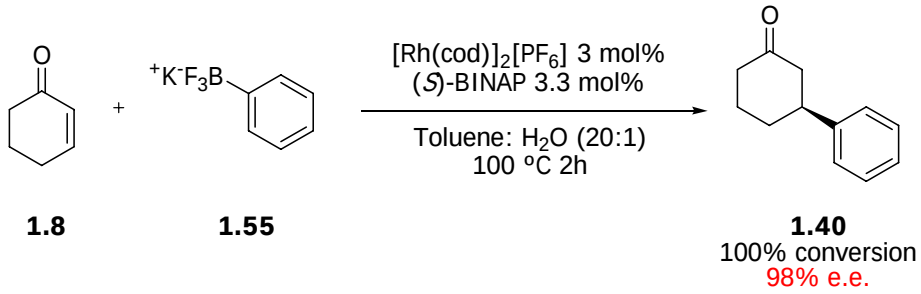
A well developed air and water stable coupling reagent is the organotrifluoroborate species as first described in 1967 by Thierig and Umland in their synthesis of potassium phenyltrifluoroborate.[78] However, it was not until 1995 that organotrifluoroborates became more wide-spread in synthetic reactions. Vedjes *et al* observed that potassium hydrogen difluoride (KHF_2) can function as a weak fluoride source in conjunction with arylboronic acids.[79] Utilising this procedure the group demonstrated the efficient conversion into potassium aryltrifluoroborates (**1.55**) on treatment with the KHF_2 in aqueous methanol yielding the products as highly stable crystalline materials. Potassium trifluoroborates allow the facile synthesis of aryl, alkynyl, alkenyl and alkyl boronate species previously unavailable with existing boron or stannane chemistry.[26] The only drawback of potassium trifluoroborates is the lack of solubility in organic solvents; however this can be rectified by counterion exchange of potassium to tetrabutylammonium (**1.54**) as described by Batey *et al*.[80] Many palladium-catalysed cross coupling reactions of trifluoroborate salts have been published especially by the groups of Genet and Molander.[81, 82]

The first rhodium-catalysed conjugate addition reactions with trifluoroborate salts were undertaken by Batey and co-workers.[83] Using MVK (**1.5**) with potassium phenyltrifluoroborate (**1.55**) in the presence of $Rh(acac)(CO)_2$ (3 mol %) and dppb, complete conversion to product (**1.7**) was observed in 16 hours. The reaction was efficient with only 1.1 eq. of boronate and allowed coupling of a range of aryl and alkenyl trifluoroborate salts, including previously problematic electron-deficient boron species such as 3-nitrophenyltrifluoroborate in good yields. The relative rate of reaction for potassium boronates was faster than the corresponding phenylboronic acid with reactions being complete in 8 hours compared to 16 hours. It was postulated that the facile transmetalation to form the active Rh-aryl species was the major reason for the improvements (*Scheme 13*).



Scheme 13

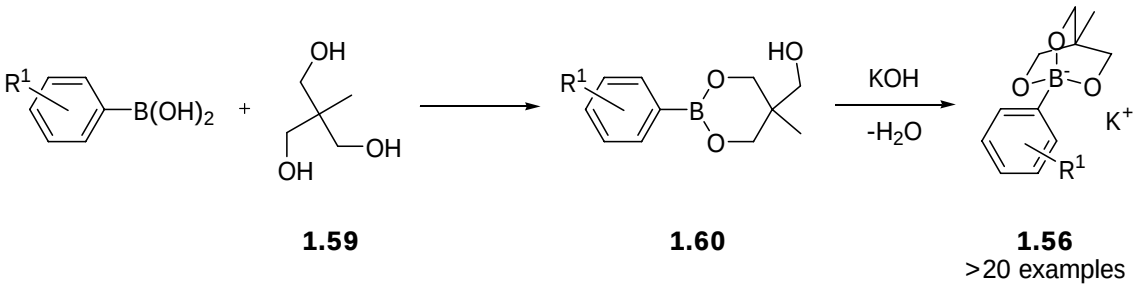
The rhodium-catalysed addition of trifluoroborate salts was expanded upon by Genet and co-workers.[28, 84] Utilising the reaction of aryl boronates in the conjugate addition to cyclohexenone (**1.8**), it was found that a range of neutral rhodium pre-cursors proved ineffectual in catalysing the reaction. However, upon switching to cationic sources such as $[Rh(cod)_2][PF_6]$, $[Rh(cod)_2][BF_4]$ and $[Rh(cod)_2][ClO_4]$, a dramatic improvement in reaction rate with complete conversion to 3-phenylcyclohexanone (**1.40**) observed in 1-2 hours at 100 ºC. The most dramatic influence on the reaction was the choice of solvent; very low e.e.'s were obtained in polar or protic solvents. Higher enantioselectivities were achieved in aprotic and non-chelating solvents such as toluene or heptane. Temperature and quantity of water also play significant roles with only racemic product observed at low temperatures, and no material isolated at extremes of water concentration (*Scheme 14*).



Scheme 14

Potassium organotrifluoroborates are currently the boronate reagent of choice for cross-coupling reactions.[82] However, there are still attempts to synthesise novel alternatives, with one of the most promising being the cyclic triolborates (**1.56**) synthesised by Miyaura *et al.*[85] These boronate reagents are exceptionally stable in air and water and more soluble in organic solvents than potassium trifluoroborates. Synthesis involves the condensation of boronic acids with 1,1,1-tris(hydroxymethyl) ethane (**1.59**), with subsequent complexation of the boronic

ether species (**1.60**) with potassium or tetrabutylammonium hydroxide giving the precipitated product in high yields. Such boronates have been shown to give excellent results in both palladium-catalysed Suzuki couplings and copper-catalysed amination chemistry. The triolborates are tolerant to air, water and base and allows a range of heteroaromatic rings such a pyridine and furan to be coupled in high yields with only 1.1 eq. of organometallic reagent (*Scheme 15*).



1.59 **1.60** **1.56**
>20 examples

Scheme 15

1.3 Substrate & Organometallic Variation

1.3.1 Substrates

Currently the only substrates discussed in the rhodium-catalysed conjugate addition reaction have been simple cyclic and acyclic enones. Such substrates are highly reactive and tend to give good yields and selectivity. A range of α,β-unsaturated substrates are shown below and will be discussed subsequently (*Figure 6*).

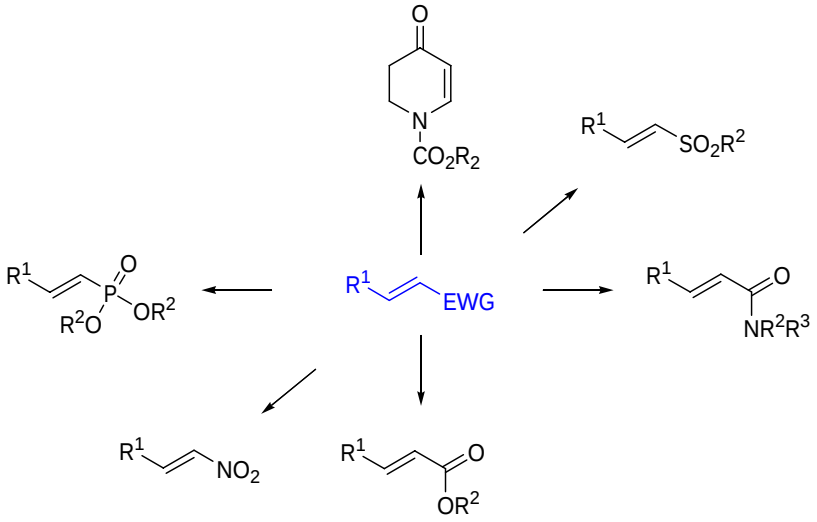
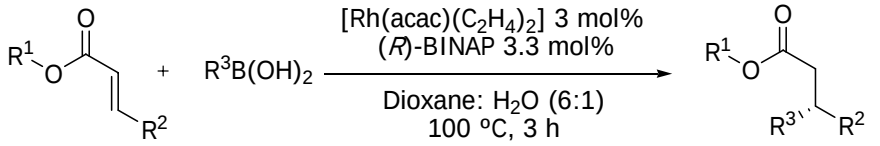


Figure 6

1.3.1.1 α,β-Unsaturated Esters

α,β-unsaturated esters (**1.61**) are the second most commonly used substrates for rhodium-catalysed additions after enones. Although they are less reactive they are still excellent materials giving α-substituted esters (**1.62**) in high yields and selectivity. Both Hayashi[86] and Miyuara[75] have undertaken routes to acyclic unsaturated esters utilising analogous conditions to previously studied enones (*Scheme 16*).

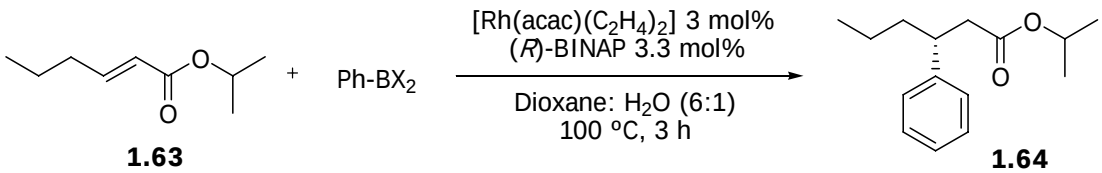


1.61
R^1 = Me, Et, iPr, Bn
R^2 = H, Alkyl, Aryl

1.62
21-98% yield
77 to 98% e.e.

Scheme 16

Although less reactive than α,β-unsaturated ketones, high enantioselectivity and yields can still be obtained by increasing reaction temperature. The other important consideration is the choice of ester group, with bulky groups such as *tert*-butyl and cyclohexyl giving excellent selectivity but low yields. This could be rectified by compromising the bulkiness of the ester to isopropyl (**1.63**) or changing the ligand type to a less sterically demanding variant such as (*S*), (*S*)-Chiraphos. Utilising *in situ* boronate chemistry outlined previously also gives better yields for the addition to α,β-unsaturated esters. Reaction of phenyl boronic acid gives a moderate yield of isopropyl 3-phenylhexanoate (**1.64**) (42%), improved to 96% with the corresponding phenyl boronate species. More recently potassium organotrifluorborates were also utilised in this process by Navarre *et al* giving good yields and selectivity using (*R*)-BINAP and cationic catalyst combinations (*Scheme 17*).[87]



1.63

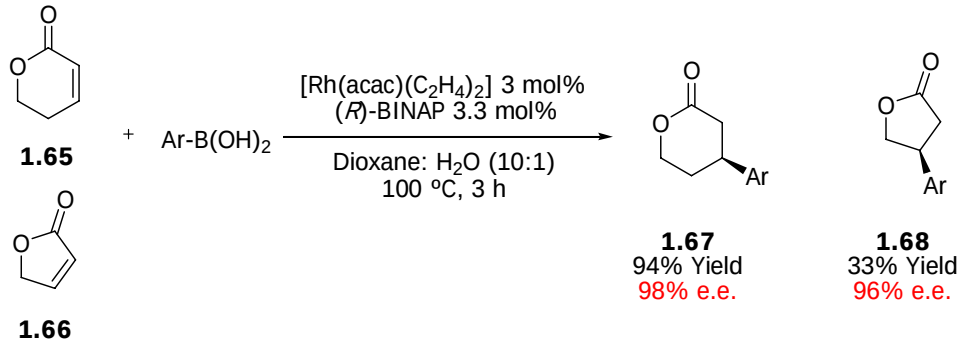
A: 5 eq Ph-$B(OH)_2$ Dioxane, H_2O 10:1
B: 2.5 eq Ph-$B(OMe)_3Li$ Dioxane, H_2O 1:1
C: 4.0 eq Ph-BF_3K Toluene, H_2O 20:1

1.64

A: 42% Yield, 94% e.e.
B: 96% Yield, 95% e.e.
C: 87% Yield, 96% e.e.

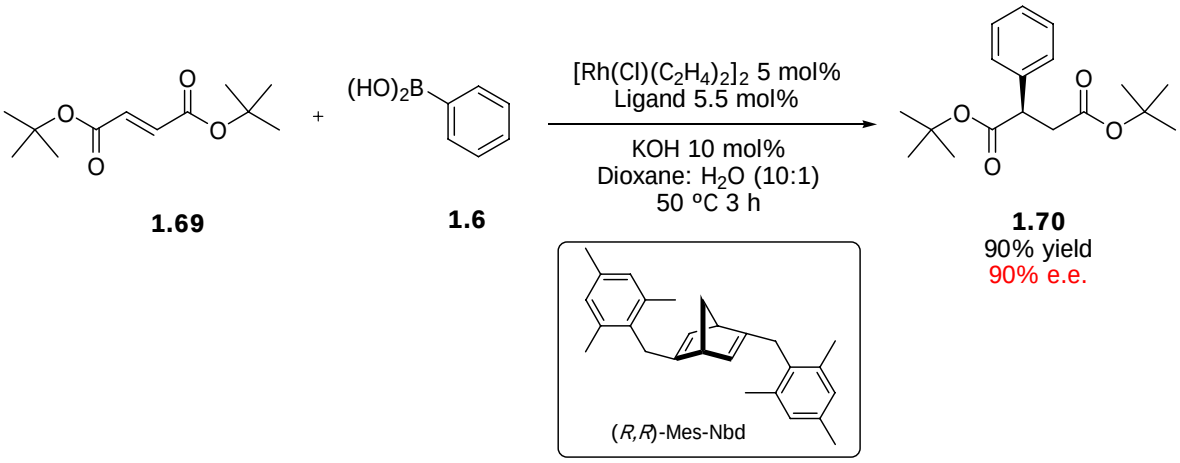
Scheme 17

Conjugate addition methodology also gives excellent enantioselectivity to cyclic lactones such as 5,6-dihydro-2H-pyran-2-one (**1.65**) and 5,6-dihydro-2H-furan-2-one (**1.66**).[86] Interestingly the boronate addition which was so effective in acyclic systems proves ineffectual for lactones. This is possibly due to the equivalents of methanol generated under elevated temperatures leading to ring opening. However, using boronic acid species gives the corresponding 4-aryl-tetrahydropyran-2-one (**1.67**) and 4-aryl-tetrahydrofuran-2-one (**1.68**) in greater than 95% e.e. Using 5-membered lactones, poor yields in the conjugate-addition reaction are obtained, this is possibly due to ring strain in the cycle making rhodium coordination and subsequent aryl insertion difficult (*Scheme 18*).



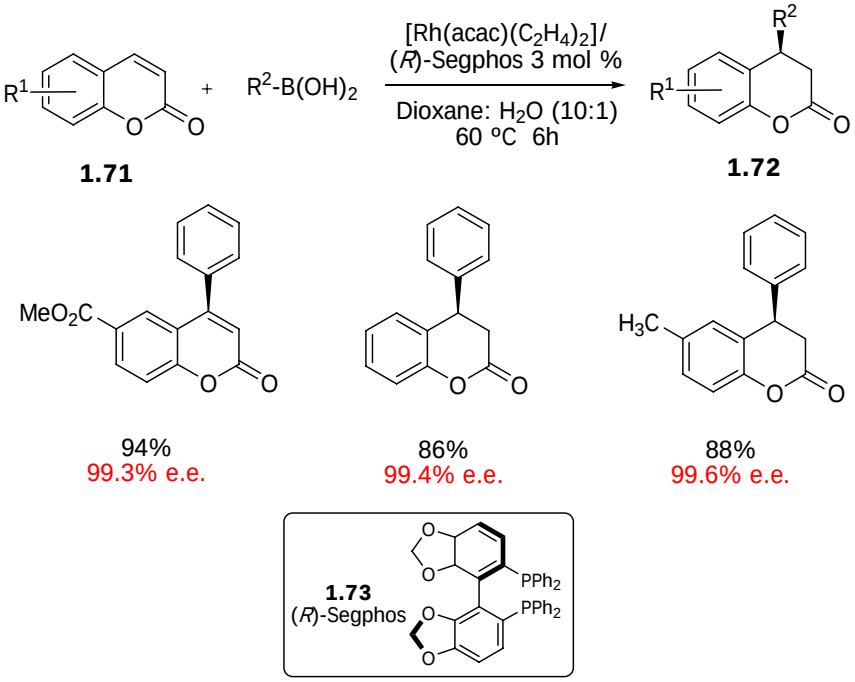
Scheme 18

Shintani *et al* have shown a rhodium-diene ligand based system allowing fumaric compounds (**1.69**) to be utilised as substrates in 1,4-addition reactions.[66] The di-*tert*-butyl 2 phenylsuccinate products (**1.70**) of these reactions have not been studied, despite the fact that 1,4-addition products of these compounds are synthetically useful 2-substituted 1,4-dicarbonyl compounds The use of chiral phosphines and phosphoramidites proved ineffective in the reaction with low yields and selectivity observed. The use of chiral dienes rectified this, although the (*R*),(*R*)-benzyl nbd derivative gave poor yields, upon changing the groups on the ligand to mesitylmethyl groups selectivity and yield improved to an acceptable level (*Scheme 19*).



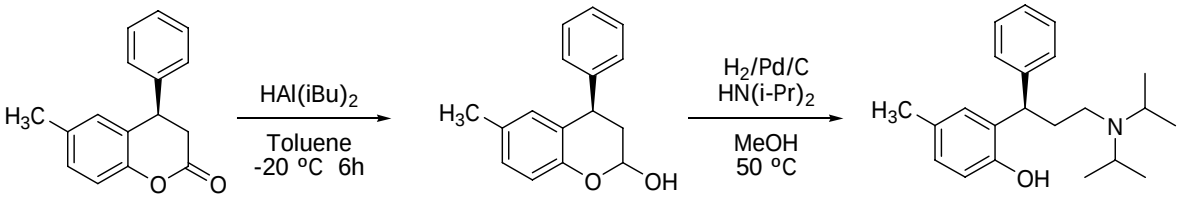
Scheme 19

Another example of conjugate addition to cyclic lactones is the use of coumarin derivatives (**1.71**) in rhodium-catalysed conjugate additions.[88] Utilising boronic acids gives 4-arylchroman-2-ones (**1.72**) with the stereogenic carbon centre at the 4-position substituted with two aryl groups. Coumarins tend to be very poor substrates for 1,4-additions, thus up to 10 equivalents of boronic acid were required for successful conversion to product. (*R*)-Segphos (**1.73**) proved to be highly effective as a chiral ligand giving >99% e.e. at 60 ºC for 6 hours (*Scheme 20*).[89]



Scheme 20

This route to 4-aryl substituted chroman-2-ones allows the asymmetric synthesis of (*R*)-tolterodine (**1.74**) an important urological drug. Utilising (*R*)-6-methyl-4-phenylchroman-2-one (**1.75**) formed *via* conjugate addition, reduction of the lactone to the lactol (**1.76**) which was then subjected to palladium-catalyzed hydrogenation in the presence of diisopropylamine to yield 91% of the final product (**1.74**) in 3 steps (*Scheme 21*).



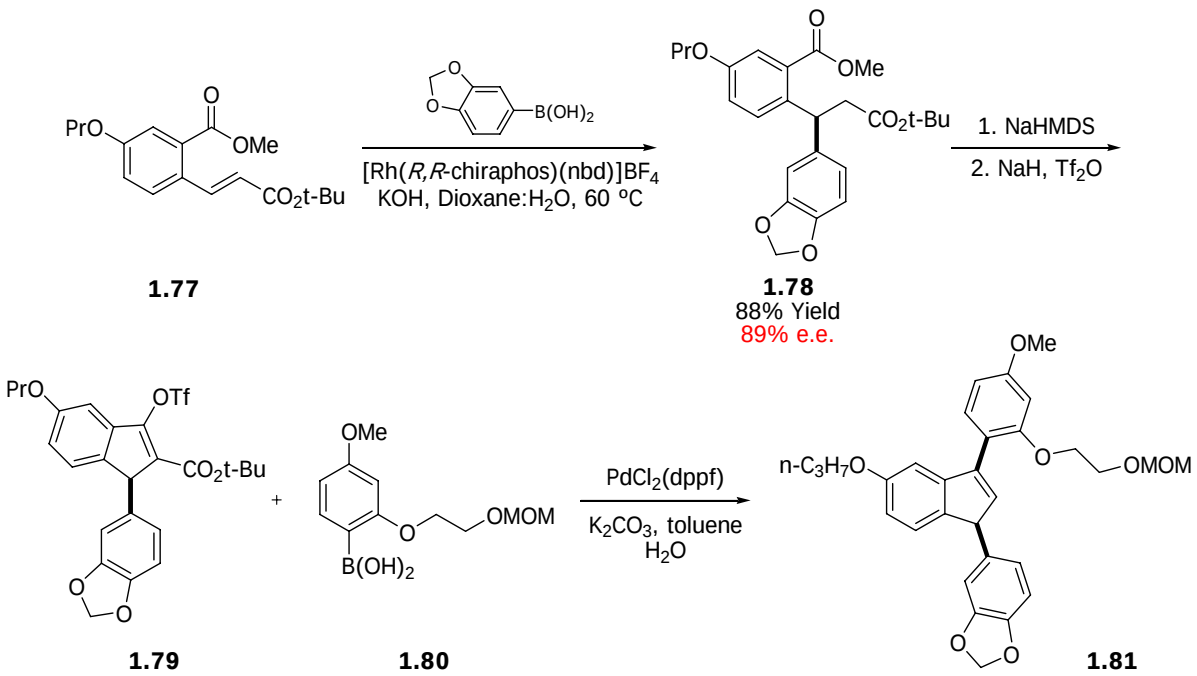
1.75
99.6% e.e.

1.76

1.74
(*R*)-Tolterodine

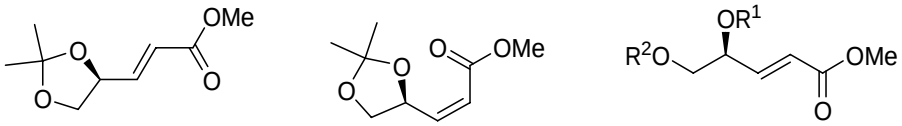
Scheme 21

Rhodium-catalysed conjugate addition has proved to be a valuable method of forming other medicinally interesting compounds. Miyuara and co-workers have used such an approach in the enantioselective synthesis of endothelin receptor antagonists.[90] The example attempted was of endothelin receptor antagonists reported by SmithKline Beecham. Initial attempts of the conjugate-addition to benzo-fused 2-cyclopentenone derivatives, gave poor results with the best yield being 28% after extensive screening, selectivity was low at 8% e.e. The alternative route involved α,β-unsaturated ester formation by Heck coupling of with *tert*-butyl acrylate with the corresponding methyl 2-bromo-5-propoxybenzoate (**1.77**). The desired conjugate-addition product (**1.78**) was then obtained in 89% e.e. with (*R,R*)-chiraphos as the optimum chiral ligand in conjunction with $[Rh(nbd)_2][BF_4]$. Final steps to the desired compound included the Claisen cyclisation of with sodium hexamethyldisilazide (NaHMDS) yielding the substituted cyclopentene derivative. Next steps involved enolate formation and sulfonylation with trifluoromethane sulfonic anhydride to yield triflate (**1.79**) in 72% over 2 steps. This was subjected to Suzuki coupling with previously formed 4-methoxy-2-(2-(methoxymethoxy) ethoxy)phenylboronic acid (**1.80**) to give key endothelin antagonist intermediate (**1.81**) in 90% yield, with 3 further steps finalising the synthesis (*Scheme 22*).



Scheme 22

Csaky and co-workers have shown that acyclic γ,δ-oxygen-substituted α,β-enoates (**1.82-1.87**) can be utilised as chiral substrates in conjugate-addition reactions.[91] These substrates give a different perspective in rhodium catalysed reactions as the chiral substrate should control the stereoselectivity of the reaction and not a chiral ligand. Traditionally γ,δ-oxygen-substituted compounds have been considered as poor substrates for conjugate addition reactions, as oxygen at the γ-position makes the β-carbon less electrophilic than ordinary α,β-unsaturated esters (*Figure 7*).

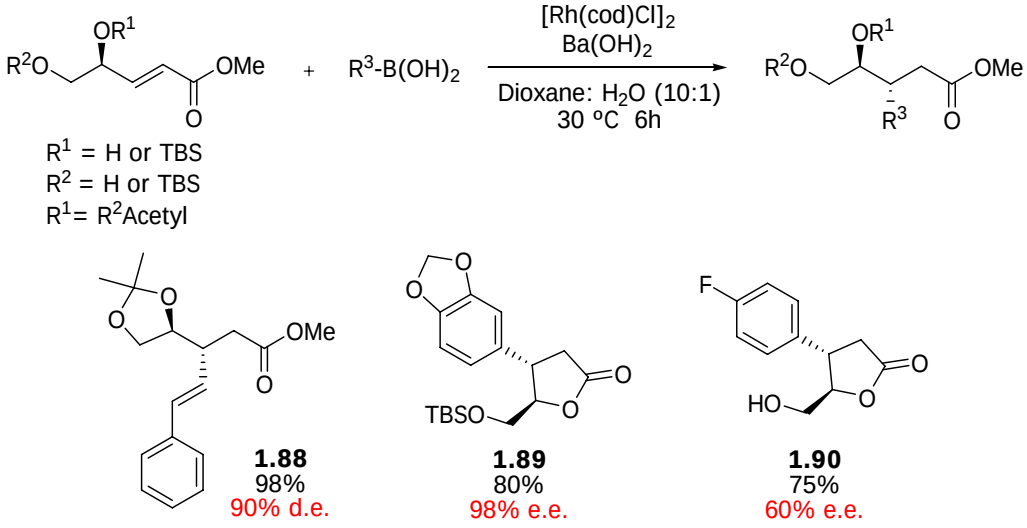


1.82 **1.83** **1.84, 1.85** R^1 = H or TBS **1.86, 1.87** R^2 = H or TBS

Figure 7

Substrates are readily prepared from *D*-glyceraldehyde acetonide with the corresponding acetyl or TBS ether protecting groups previously incorporated. Of special interest are the free hydroxyl substrates, as traditional organocuprate chemistry is intolerant of such functional groups. Thus using $[Rh(cod)Cl]_2$ and a suitable base such as barium hydroxide allows boronic

acid addition to occur in good yield with excellent *anti* selectivity (**1.88**). Some interesting results are observed dependant on the protecting groups present on the substrate. Compounds with an unprotected γ-hydroxyl group react with aryl- and alkenyl boronic acids to afford *trans*-lactones with good selectivity (**1.89-1.90**). This result was also observed for substrates with both δ and γ-hydroxyl groups unprotected, however, selectivity is reduced; this is proposed to be due to chelation effects of the δ-hydroxyl group. Substrates that have both alcohol motifs protected with bulky TBS groups give no selectivity, although yields are good (*Scheme 23*).



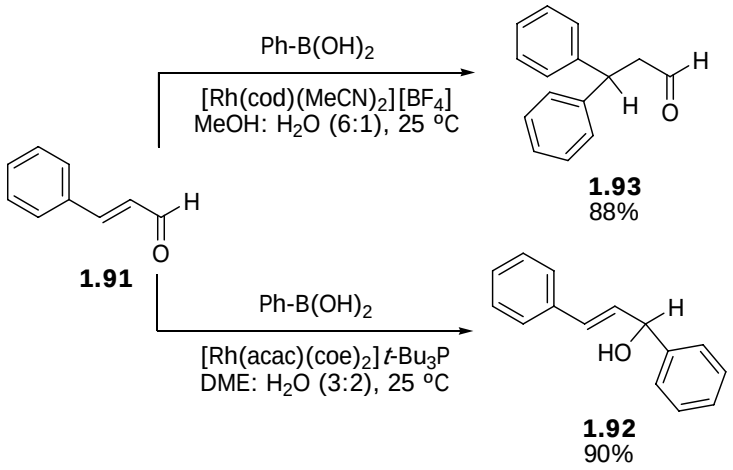
Scheme 23

1.3.1.2 α,β-Unsaturated Aldehydes

One of the more problematic substrates in rhodium-catalysed conjugate addition chemistry is the addition to α,β-unsaturated aldehydes, due to competing 1,2- and 1,4-addition reactions. The rhodium-catalysed addition of boron species to aldehydes in a 1,2-fashion is well documented and understood with many groups contributing to the field.[83, 92-94] Despite the bulk of literature in the area, the synthesis of α-α′-diaryl substituted aldehydes has received little attention until recently.

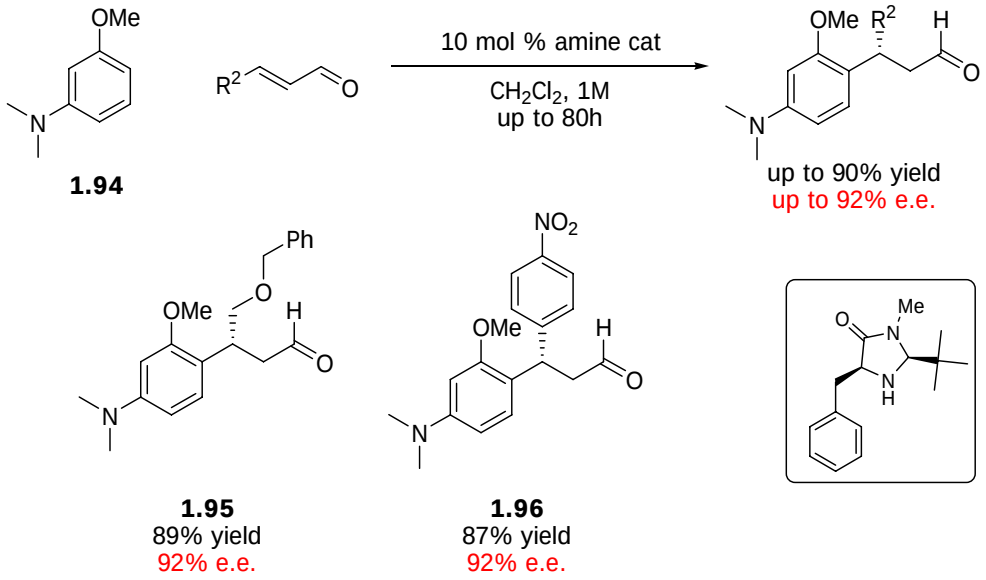
Miyaura published the seminal work on conjugate-additions to α,β-unsaturated aldehydes with the addition of phenyl boronic acid (**1.6**) to *trans*-cinnamaldehyde (**1.91**).[95] It was observed that bulky monodentate phosphine ligands gave primarily the 1,2-addition product (**1.92**) in

α,β-unsaturated systems. The electronics and stoichiometry of the ligand were key factors in the reaction, with highly electron donating phosphines such as tri(isopropyl)phosphine and tri(tert-butyl)phosphine (*t*-Bu_3P) giving excellent yields. No conversion was observed with greater than 3 equivalents of ligand to rhodium, due to the basicity of the phosphine utilised. For the conjugate-addition product (**1.93**) the *t*-Bu_3P complex yielded solely the 1,2-addition product. The 1,4-addition reaction was catalysed by a cationic rhodium complex in aqueous dimethoxyethane (DME) giving a mixture of conjugate and 1,2-addition products at 50 °C. A single product could be obtained at room temperature with aqueous methanol as a solvent. No attempts to obtain enantioselective products were undertaken (*Scheme 24*).



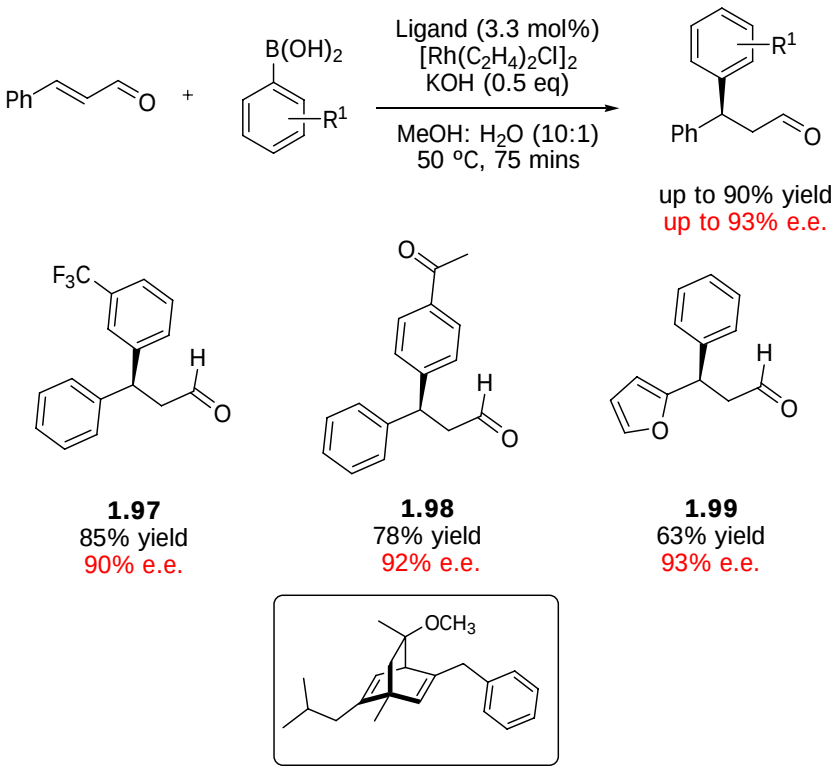
Scheme 24

Before 2006 the main method of forming the an asymmetric 3,3′ biaryl propanal motif was by amine organocatalysis pioneered by MacMillan *et al.*[96] The reaction occurs *via* the reversible formation of chiral-iminium ions allowing the carbon-carbon coupling of electron rich aryl species. The synthesis of electron-rich aniline species such as 3-methoxy-*N*,*N*-dimethylbenzenamine (**1.94**) is a useful tool and can be achieved with only a 1 mol% loading of amine organocatalyst in 88% e.e. The synthesis is limited with only a few structures accessible (**1.95-1.96**). The reaction is intolerant to water and substituted benzene motifs are more preferable to the aniline functional groups (*Scheme 25*).



Scheme 25

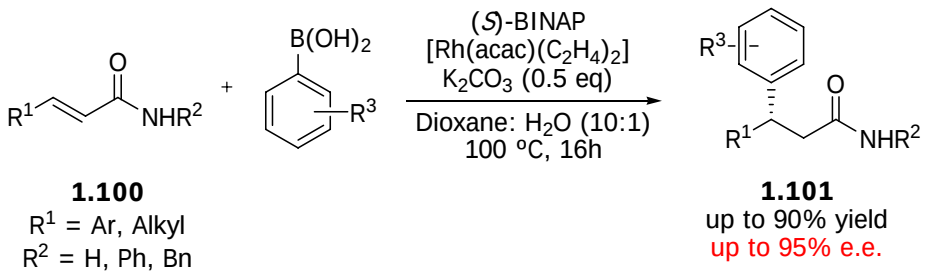
Asymmetric rhodium-catalysed 1,4-addition to enals had been reported by Itooka and co-workers in modest yield utilising a [Rh((*R*)-BINAP)(nbd)][BF_4] catalyst system, although selectivity was low.[30] The groups of Carreira and Hayashi have independently observed that chiral diene ligand systems have been the major breakthrough in conjugate addition to α,β-unsaturated aldehydes.[67, 97] Carreira has used chiral diene ligands based on optically pure carvone derivatives, in the addition of substituted boronic acids to enals.[98] The group showed that chiral phosphines such as (*R*)-BINAP gave good selectivity in the reaction (89% e.e.) but poor yields. In contrast chiral dienes allowed the coupling of electron-rich and electron-deficient boronic acids successfully (**1.97-1.99**) and high e.e (88%). Both enantiomers of a given building block can be obtained by varying the donor and acceptor using a single enantiomer of the ligand (*Scheme 26*).



Scheme 26

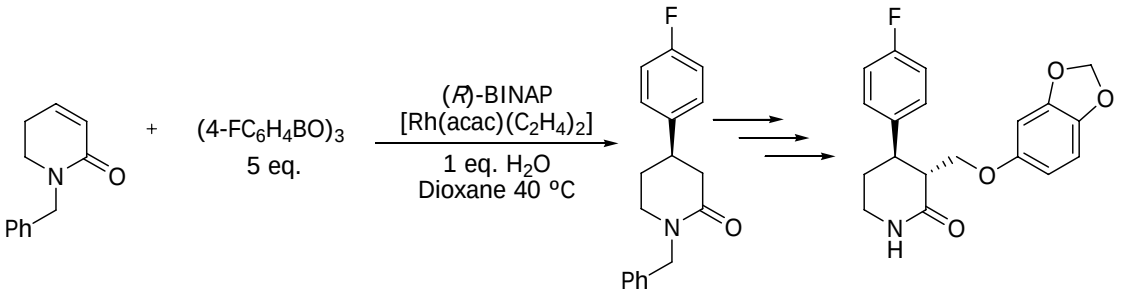
1.3.1.3 α,β-Unsaturated Amides and Piperidones

Some of the most sought after intermediates involve nitrogen containing groups or ring systems. Rhodium-catalysed addition of boronic acids has been conducted to species such as sulfinimines[99] and isocyanates[100, 101] with excellent success. The conjugate addition to α,β-unsaturated amides (**1.100**) yielding aryl amides (3-phenylbutanamide) has been studied initially by the groups of Hayashi[102] and Miyuara.[103] The conditions were analogous to previous reactions to acyclic ketones and esters, with a rhodium-BINAP mixture and addition of an inorganic base such as potassium carbonate (*Scheme 27*).



Scheme 27

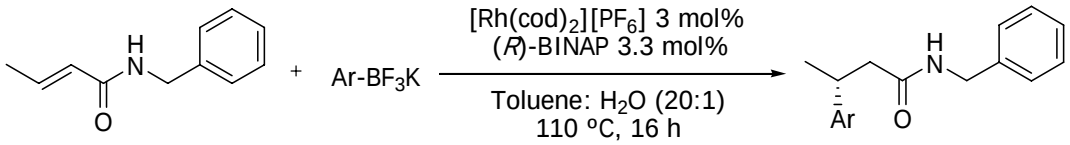
Changing the organoboron species to organoboroxines allows access to 4-aryl-2-piperidinones, formed from the corresponding protected lactams. These species are especially sought after due to their medicinal properties. Conjugate-addition reaction to 5,6-dihydro-2-(1*H*)-pyridinones (**1.102**) 4-fluorophenylboroxine (**1.103**) allow the formation of a key intermediate (**1.104**) in the synthesis of anti-depressant and anti Parkinson's disease drug (-)-Paroxetine (**1.105**) (*Scheme 28*).[104]



1.102 **1.103** **1.104** 63% yield 97% e.e. **1.105** (-)-Paroxetine

Scheme 28

Potassium trifluoroborate salts have also been successfully utilised in conjugate additions to α,β-unsaturated amides (**1.106**).[105] Previously used cationic rhodium salts were used in conjunction with (*R*)-BINAP in a toluene water mixture giving enantioenriched aryl and alkenyl products (**1.107**) in high yields. Comparison the reactivity of boronic acid and trifluoroborate salts found that the borate species give rapid conversion to product with over 90% conversion in 1 hour. Addition of base was also studied showing an accelerating effect for boronic acids, but a large decrease in selectivity for arylborate species (*Scheme 29*).

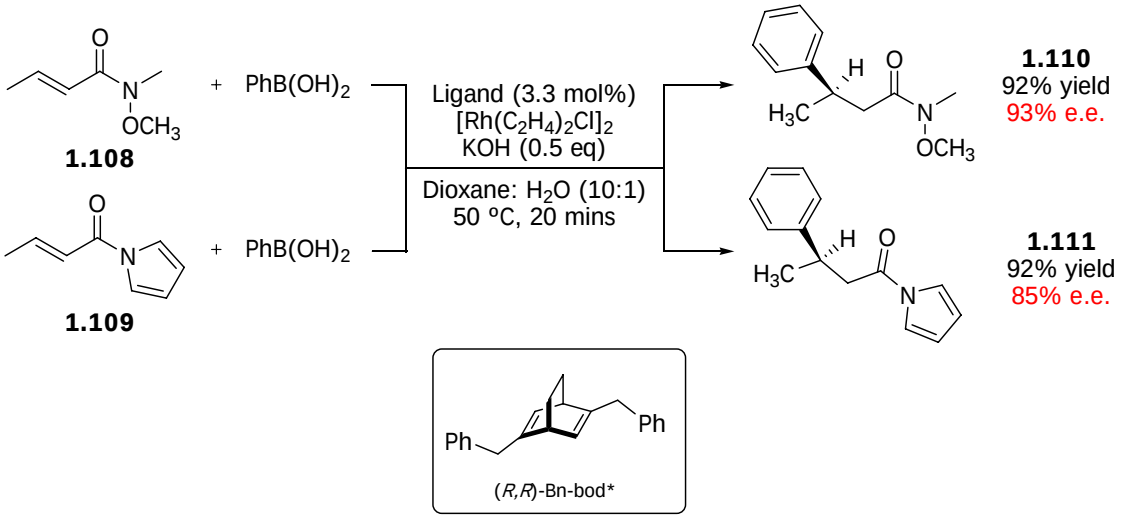


1.106 **1.107** up to 100% yield up to 95% e.e.

Scheme 29

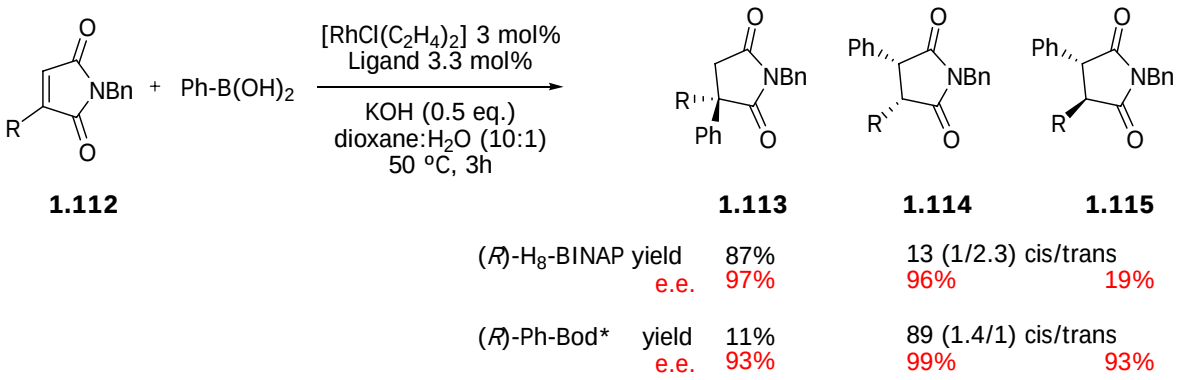
Two of the most synthetically important amides are Weinreb amides (**1.108**) and N-acyl pyrroles (**1.109**) as they are excellent acylating agents. Hayashi has efficiently constructed Weinreb amides bearing β-stereogenic centres (**1.110**) in a highly enantio-enriched form

utilising a rhodium-diene strategy.[68] The yields and selectivity are excellent and the system is general for a number of amide substrates including N-acyl pyrroles (**1.111**) and crotamides. Further manipulations of Weinreb amides give the corresponding esters, ketones or aldehydes with no loss of selectivity at the β-carbon (*Scheme 30*).



Scheme 30

Enantioselective construction of all carbon-quaternary centres is an important challenge in rhodium-catalysed conjugate additions. Maleimides (**1.112**) have proved to be an effective substrate for conjugate addition with both protected[66] and unprotected amides[106] proving successful. The development of a rhodium-catalysed asymmetric 1,4- addition of arylboronic acids to 3-substituted maleimides furnishing 3,3′-disubstituted succinimides in high regio- and enantioselectivity has been described by Shintani *et al.*[69] The reaction displays an interesting ligand effect. The reactions are carried out in identical conditions with a neutral rhodium source and base being required for high turnover of catalyst. The observed regioselectivity in these 1,4-additions can be explained by the severe steric repulsions between the substituent R on maleimide and the phenyl group using (*R*)-H_8-BINAP. Thus preferential coordination to rhodium to the maleimide minimises steric repulsions of the *R*-group and ligand giving preferential formation of the 3,3′ substituted product (**1.113**). In contrast using chiral diene (*R*)-Ph-Bod* the orientation of the phenyl substituent on the ligand reduces the steric repulsion with the R- group. As a result, the steric hindrance between the aryl group on the rhodium and the R group on maleimide becomes the overriding factor, leading to selective insertion of maleimide toward the formation of 2,3 *bis*-substituted products (**1.114-1.115**) *(Scheme 31)*.



Scheme 31

Orthogonally substituted α,β-unsaturated compounds such as 4-oxobutenamides (**1.116**) provide an alternative synthetic challenge in Michael addition chemistry. In general routes to 2-aryl-4-oxobutanamides are limited with difficulty in achieving the correct regioselectivity. Work by Zigterman *et al* have addressed this problem with conjugate additions of organoboronic acids to oxobutenamides, this requires a catalyst system that distinguishes not only enantiotopic π-faces but also the subtle electronic differences of each conjugate acceptor (*Figure 8*).[107]

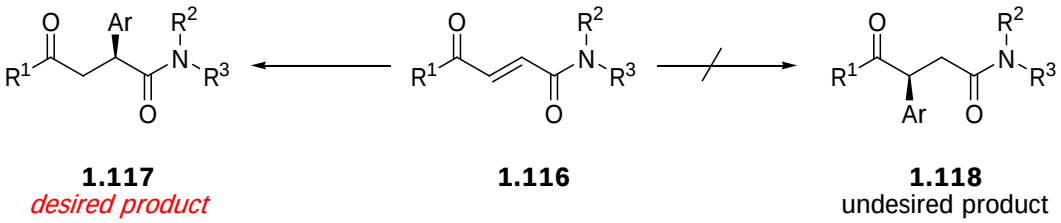
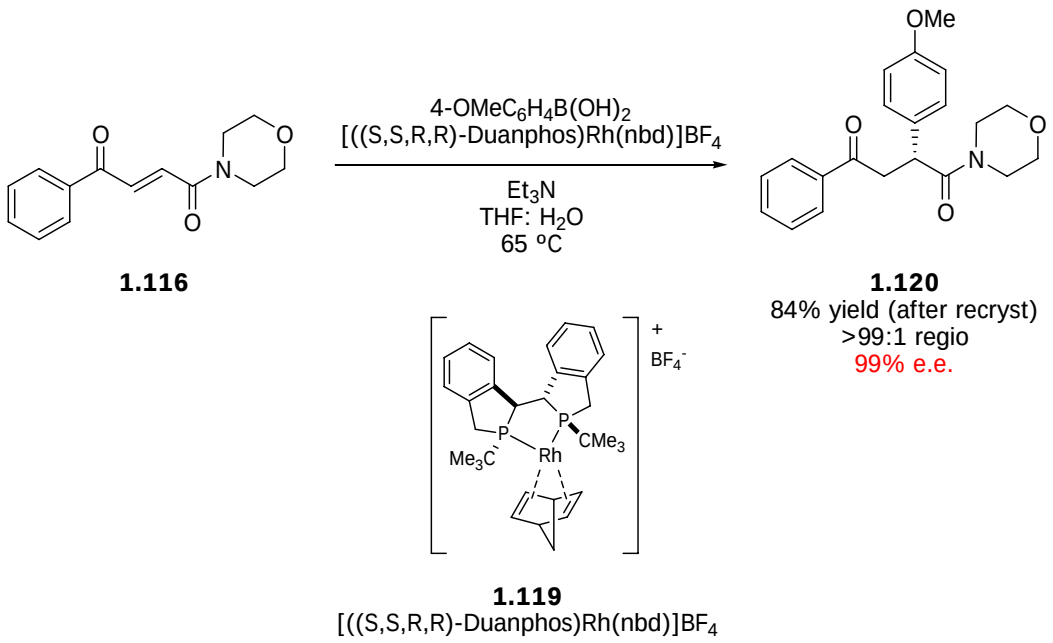


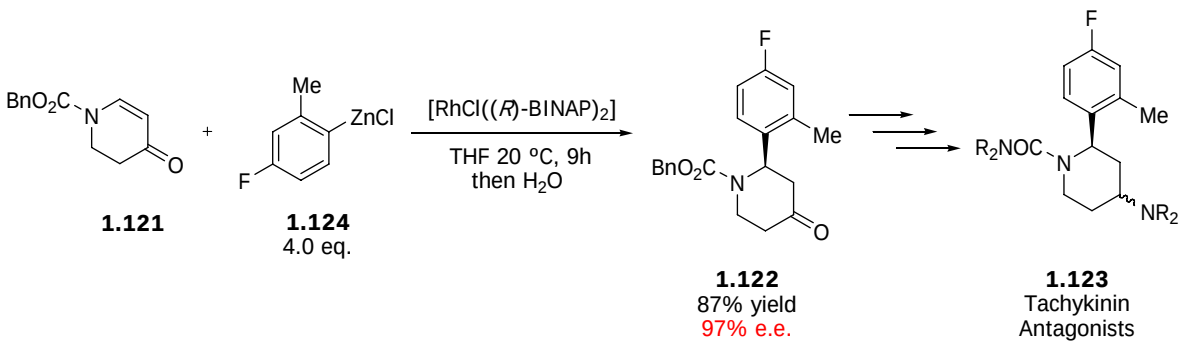
Figure 8

The conditions were thoroughly optimised with bisphosphines such as BINAP and *tol*-BINAP giving good enantioselectivity but regioselectivity of 9:1 in favour of 2-aryl-4-oxobutanamide products (**1.117**) over the 3-aryl isomer (**1.118**). In contrast a chiral rhodium complex with sterically bulky P-chiral phosphines such as Tangphos[108] and Duanphos (**1.119**)[109] afforded excellent enantioselectivity while still maintaining high regioselectivity, delivering the desired (*R*)-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione regioisomer (**1.120**) in >99:1 and 95-98% e.e. (*Scheme 32*).



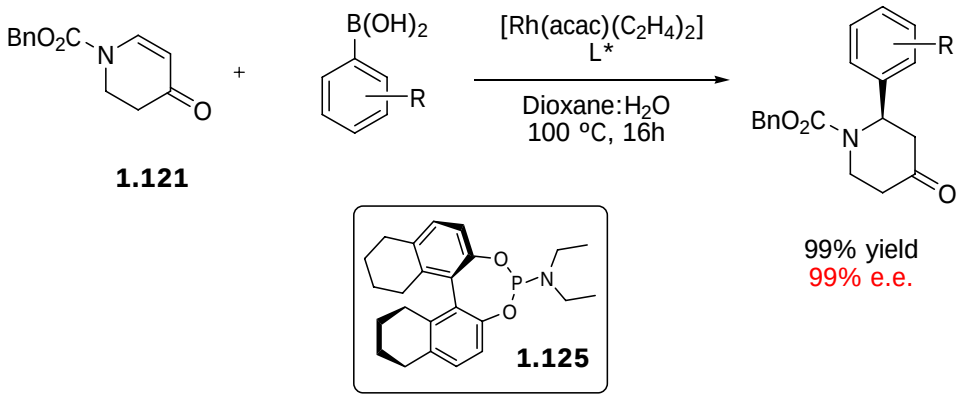
Scheme 32

The other major class of nitrogen containing α,β-unsaturated structures are the piperidones (**1.121**), which can be utilised to form the corresponding 2-alkenyl and aryl-4-piperidones (**1.122**). Organozinc reagents are becoming increasingly popular nucleophiles in conjugate-addition chemistry and an early example of their use was proposed by Hayashi in their asymmetric synthesis of tachykinin antagonists developed by GSK (**1.123**).[110] The reaction occurs under very mild conditions without any undesired 1,2-addition product observed. The 2-methyl-4-fluorophenyl organozinc nucleophiles (**1.124**) allow sterically and electronically diverse aryl groups to be added in high yields and selectivity compared to boronic acid and aryltitanium species. The reaction can also be extended to utilise substituted 4-quinolone structures giving the corresponding 2-aryl-2,3-dihydro-4-quinolones with excellent success (*Scheme 33*).[111]



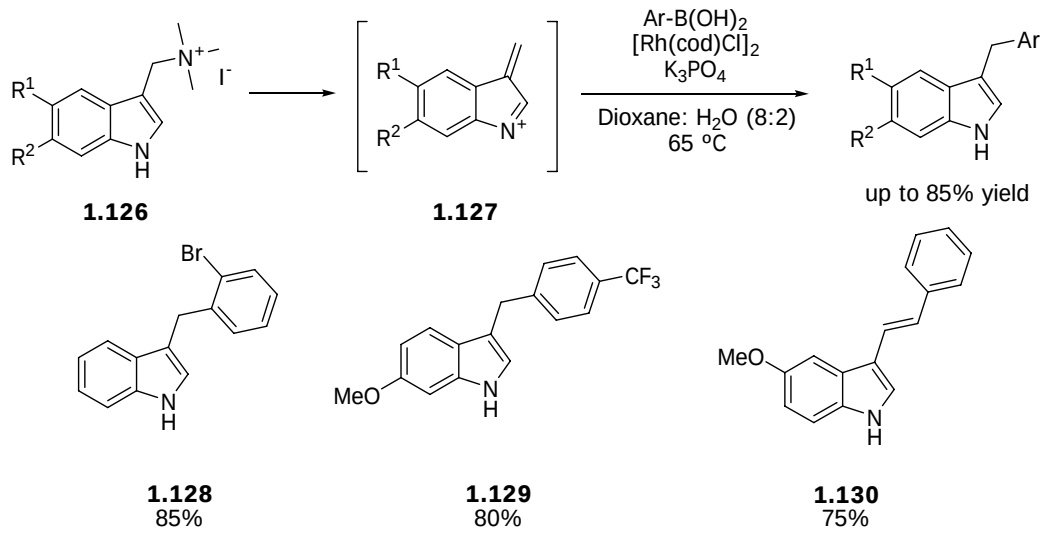
Scheme 33

Piperidone motifs have also been prepared by organostannane[112] and organoboroxime methods. Feringa has shown the chiral phosphoramidite ligands (**1.125**) provide excellent selectivity in the addition of organoboronic acids and organoboroximes to 2,3-dihydro-4-pyridones.[113] Although the substrate is not as reactive as other cyclic unsaturated carbonyl compounds, reactions still proceed with high yields and selectivity. It was found that although boronic acids could be used, their conversion to product was limited to 80%. Utilising phenyl boroxime with slow addition of water gave the product in high yields whilst retaining the excellent enantiomeric excess (*Scheme 34*).



Scheme 34

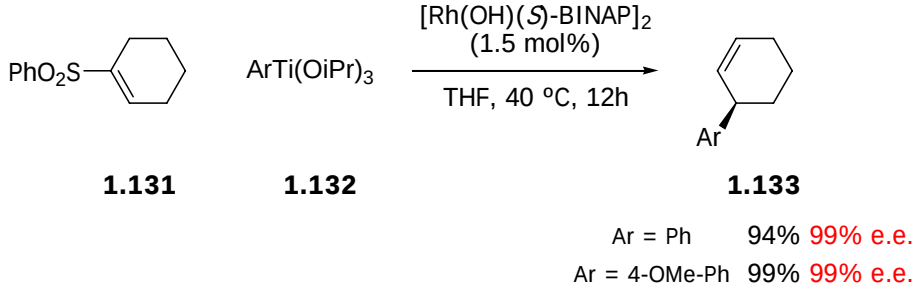
Gramines (3-aminomethylindoles) (**1.126**) can also be used in conjugate addition reactions. Such compounds can readily undergo retro-Mannich reactions at high temperatures with the alkene formed *in-situ* (**1.127**) able to undergo nucleophilic substitution. De la Herran and co-workers have provided a successful route to benzylic substitution of indoles (**1.128-1.130**) by quaternising the amino group into the trimethyliodide species, allowing the tandem retro-Mannich, conjugate-addition to occur in high yields (*Scheme 35*).[114]



Scheme 35

1.3.1.4 α,β-Unsaturated Thioesters and Sulfones

In 2003 Hayashi published the seminal work on tandem-addition elimination reactions to α,β-unsaturated sulfones (**1.131**).[115] Aryltitanium reagents (**1.132**) were utilised and had previously shown potential in the addition of aryl groups to cyclohexenone.[116] Using a hydroxy-rhodium complex in THF a new type of *cine*-substitution was observed where the sulfonyl group is eliminated after the carborhodation step generating the chiral -1-(cyclohex-2-enyl)-4-aryl compound (**1.133**) (*Scheme 36*).



Scheme 36

The proposed mechanism involves the formation of an aryl-rhodium complex which undergoes insertion into the substrate (**1.134**) followed by metal coordination to the alkene (**1.135**). In the reaction of cyclic alkenyl sulfone, the asymmetric carbon centre created at the carbo-rhodation step is retained in the substitution product (**1.136**). The favoured pathway for

rhodium-elimination is by removal of the sulfonyl group forming the corresponding allylic arene product (**1.133**) (*Figure 9*).

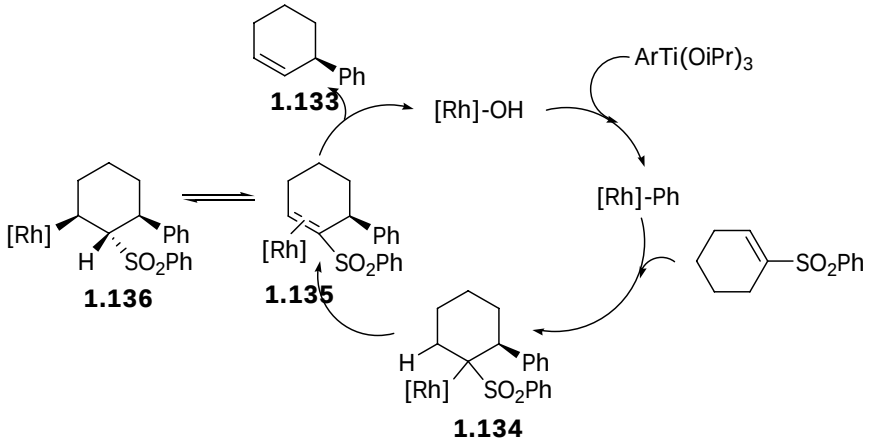
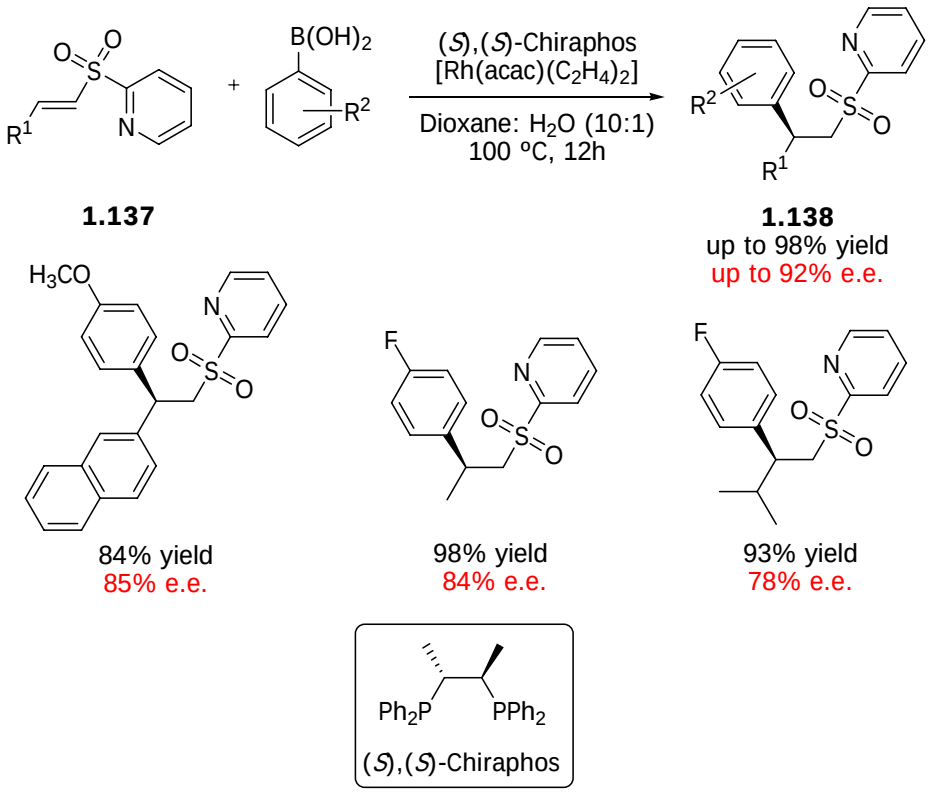


Figure 9

Conjugate-addition had still not given the desired α,β-unsaturated sulfone products. Carretero and co-workers have rectified this problem by using a suitable metal-chelate effect, which can be used to enhance the reactivity of sulfone substrates.[117] Using a rhodium-chiraphos ligand system and a 2-pyridylsulfone substrate (**1.137**) system high yields and selectivity of the β-aryl sulfone products could be obtained (**1.138**). In addition to this subsequent Julia-Kociensky olefination reaction[118] could be achieved allowing the formation of an alkene moiety in high *E:Z* ratio with no loss in selectivity at the β-position of the molecule (*Scheme 37*).



Scheme 37

Using DFT studies the mechanism is believed to occur *via* a transmetallation pathway followed by insertion of the aryl fragment through which the formation of a five-membered pyridyl-rhodium chelate species occurs (**1.139**). However, the steps leading up to insertion remain unclear. The most energetically favourable pathways involve either the coordination of the rhodium to the alkene (**1.140**) or pyridine (**1.141**) before aryl transfer. The formation of rhodium complexes attached through both nitrogen atom and alkene were not observed. Aryl transfer is stabilised by rhodium-nitrogen coordination leading to good selectivity (*Figure 10*).

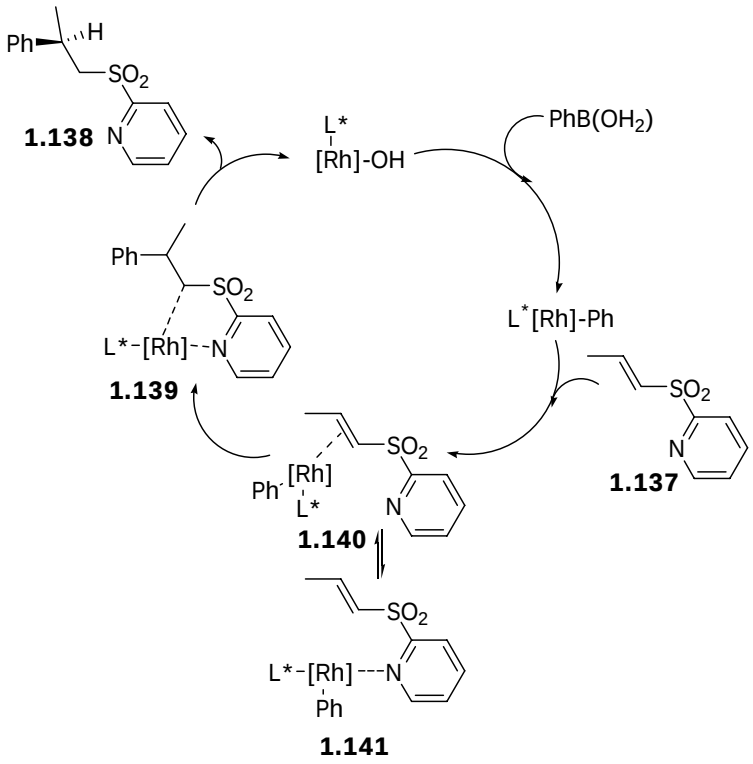
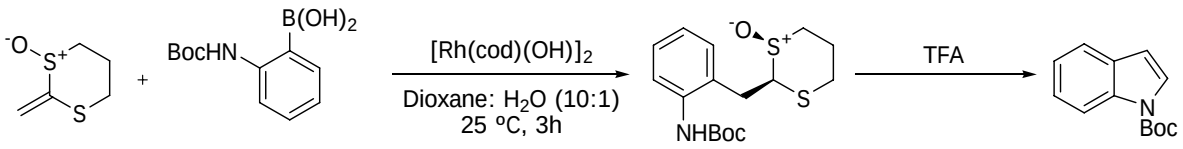


Figure 10

The final addition of sulfur containing α,β-unsaturated compounds is the addition of aryl boronic acids to ketene dithioacetal (**1.142**) by Oshima *et al.*[119] Such compounds are synthetically useful due to their ability to act as a ketene derivative. Using a mild catalyst system at room temperature the reaction occurs in quantitative yield, with only the *cis* product (**1.143**) being observed upon isolation. The corresponding products are 2-arylalkanal equivalents, and can be used in a number of further transformations including ketone and cyclic acetyl formation. Use of 2-N-Boc aniline boronic acid (**1.144**) and subsequent deprotection with trifluoroacetic acid led to quantitative formation of *N*-Boc protected indoles (**1.145**) (*Scheme 38*).

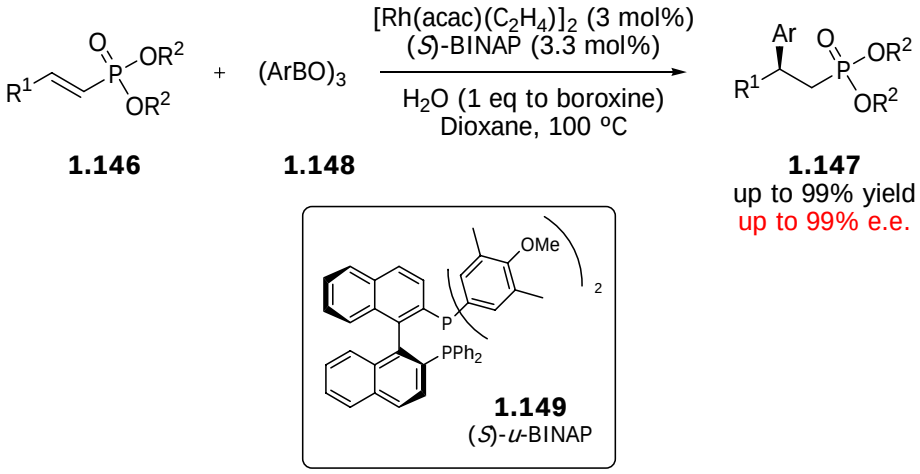


1.142 **1.144** **1.143** up to 100% yield **1.145** quant.

Scheme 38

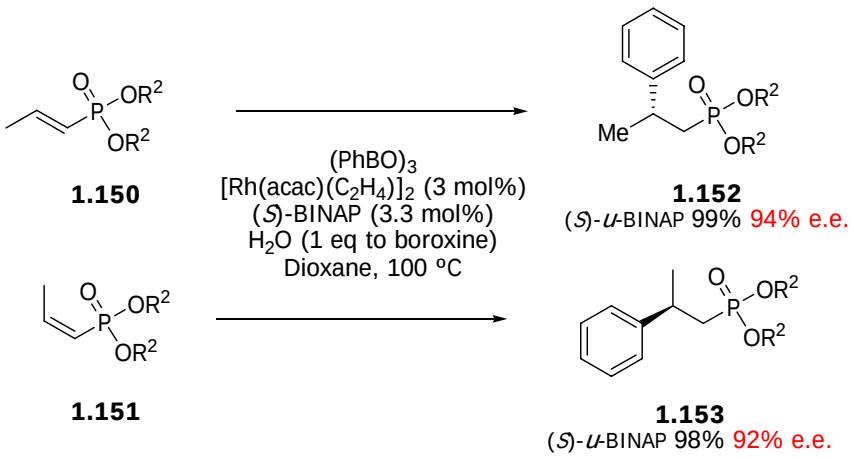
1.3.1.5 α,β-Unsaturated Phosphines

Enantioenriched phosphonic acid derivatives (**1.146**) are synthetically useful building blocks with a wide range of potential applications. Utilising rhodium-catalysed additions such molecules can be constructed *via* organoboronic acid coupling to α,β-unsaturated phosphonates (**1.147**).[120] Optimum results occur by use of aryl boroxines (**1.148**) as arylating reagents in place of arylboronic acids. High selectivity was achieved using (*S*)-BINAP in the reaction, however, improvements were observed when more sterically demanding ligands such as μ-BINAP (**1.149**) were used (*Scheme 39*).



Scheme 39

The geometry of the alkene was also studied, with isomerically pure (*E*)- (**1.150**) and (*Z*)-diethyl-1 propenylphosphonates (**1.151**) synthesised. It was found that using the same isomer of ligand gave two distinctive enantioenriched phosphonic acid derivatives, with the (*E*) isomer giving (S)- enantiomer (**1.152**) and (*Z*)- giving (*R*)- (**1.153**) respectively. This suggests the phenyl group is transferred on the same face of the substrate and the facial differentiation is thus not carried out by the position of the methyl group but by the phosphonate. The group explain the slight difference in enantiomeric excess observed between the two phosphonates by slow isomerisation of the (*Z*)-isomer to more stable (*E*)-product (*Scheme 40*).

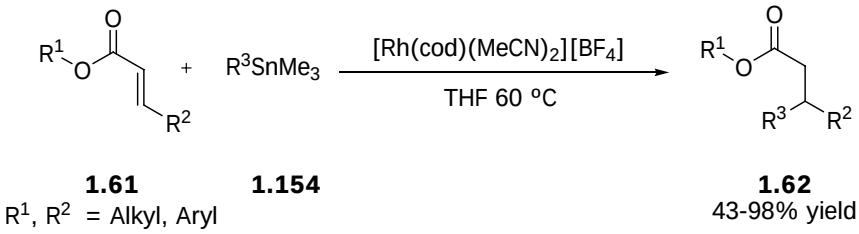


Scheme 40

1.4 Organometallics

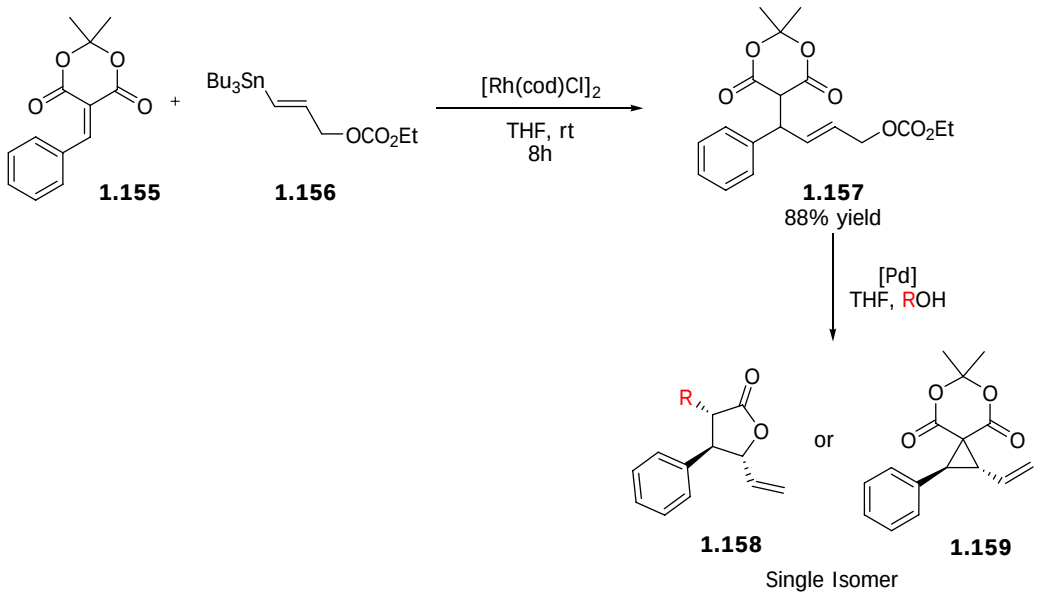
Boron derivatives have been the organometallic reagent of choice for conjugate addition chemistry. In conjuction with this other organometallic reagents have been developed for use in rhodium-catalysed 1,4-addition reactions. Materials commonly used in cross coupling reactions such as organostannanes, siloxanes and zinc reagents can also be applied to the conjugate addition of aryl and alkenyl groups to enones. Many of the more reactive organometallic reagents such as aryl titanium and zinc species readily participate in rhodium-catalysed tandem processes which will be discussed in further detail in *Chapter 2*. Finally a range of less known reagents such as organobismuth,[121] indium[122] and lead[123] have also been utilised in air and water stable reactions albeit as non-asymmetric processes.

Organostannane reagents have been well known for a number of years with their participation in the Stille coupling process as reliable coupling partners.[124] The groups of Oi and Inoue have attempted to use organotin compounds (**1.154**) in rhodium based reactions.[125] Using anhydrous conditions and low quantities of organostanne with α,β-unsaturated esters (**1.61**), good yields could be achieved. The reaction has the advantage that organotin reagents are inert to air and water however, when complexed with rhodium in the presence of D_2O the corresponding arene is rapidly formed through protonolysis (*Scheme 41*).



Scheme 41

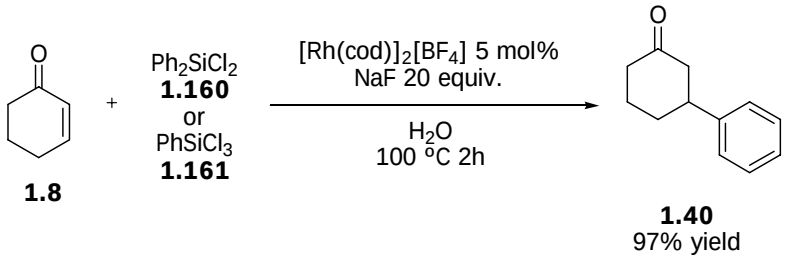
A more recent approach utilising alkenyltin reagents was achieved by Fillion and co-workers. The group uses arylidine Meldrum's Acid derivatives (**1.155**) as substrates which allow rapid addition of alkenylstannanes (**1.156**) at room temperatures in the presence of $[Rh(cod)Cl]_2$.[126] The nature and electronic character of the group present on the electrophilic carbon atom of the alkylidene malonate did not substantially affect the reactivity and (*E*)- and (*Z*)-alkene geometries were maintained (**1.157**). Meldrum's Acid also has other preferential structural properties with a readily enolisible system giving an internal nucleophile. With further optimisation of palladium intramolecular allylic carbon-carbon bond formation and oxygen-alkylation both the corresponding cyclic cyclopropane (**1.158**) and γ-butyrolactone (**1.159**) motifs could be formed as a single diastereomer in good yield (*Scheme 42*).



Scheme 42

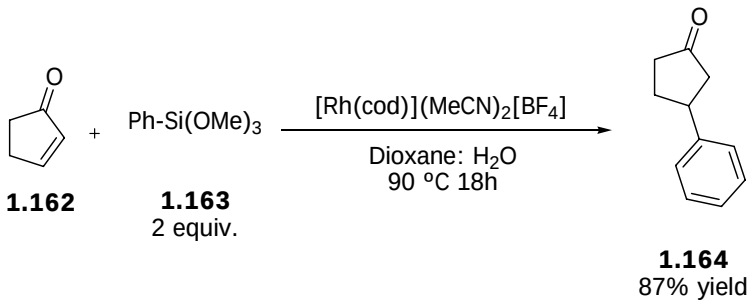
The other major organometallic reagents in conjugate addition reactions are silicon based. These compounds have been employed in a wide range of natural product syntheses and produce non-toxic byproducts based on silicone polymers.[127] Many different silicon

reagents have been prepared and evaluated in rhodium-catalysed additions including silandiols,[128] arylsilanes[129] and organosiloxanes.[130, 131] Silandiols were pioneered by Mori and co-workers in conjugate additions to methyl vinyl ketone and related unsaturated compounds.[128] They react in a non-selective way giving mixtures with the conjugate addition product and Heck type coupling in approximately equal amounts.[132] In contrast Li and co-workers have shown that di- (**1.160**) and trichloroarylsilanes (**1.161**) do react in a conjugate-addition fashion.[129] Using a cationic catalyst and sodium fluoride as a base to aid transmetallation, the desired conjugate-addition products (**1.40**) were obtained in high yield (*Scheme 43*).



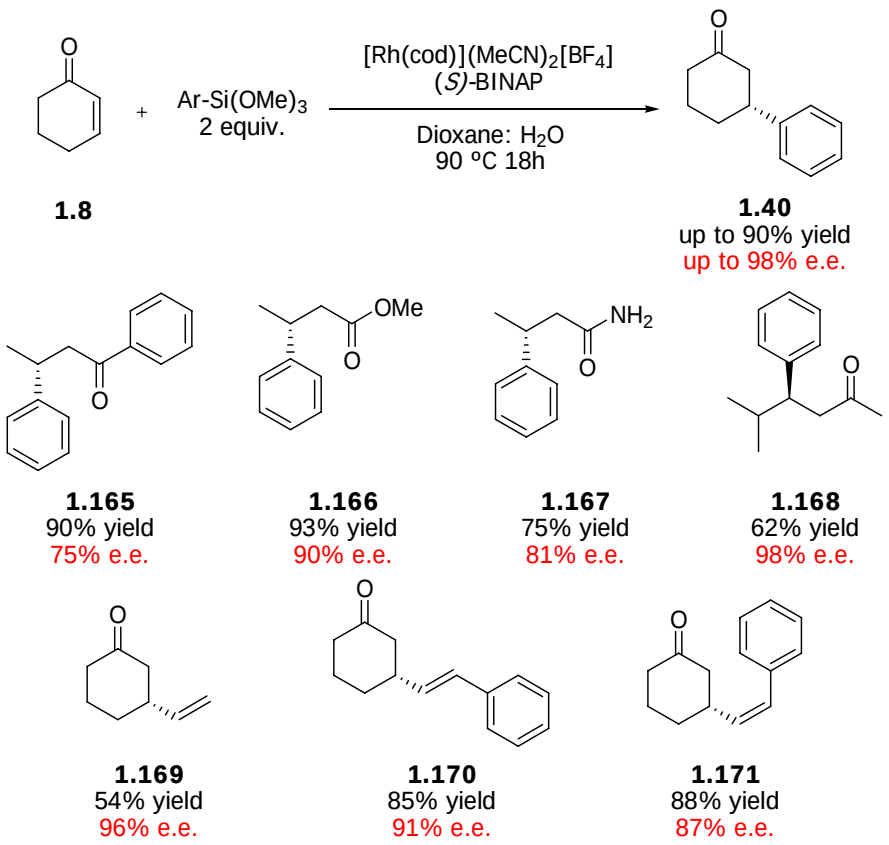
Scheme 43

Currently the most widely used silicon based organometallic reagents are the organosiloxanes, they are easy to prepare, are widely stable to air and water and readily undergo Michael addition reactions.[131] Early reports by Oi and co-workers showed that the conjugate-addition to cyclopentenone (**1.162**) could be achieved smoothly using phenyltrimethoxysiloxane (**1.163**) with a cationic catalyst in a dioxane-water mixture.[131] The reaction is believed to occur by hydrolysis of the siloxane to give the corresponding organosilanols, which were considered to be the participating silicon reagents. In a separate experiment phenylsilanetriol was prepared and gave the 3-phenylcyclopentanone (**1.164**) conjugate-addition product in 96% yield. A range of unsaturated substrates could be used including esters, amides and nitrile compounds with good yields observed throughout (*Scheme 44*).



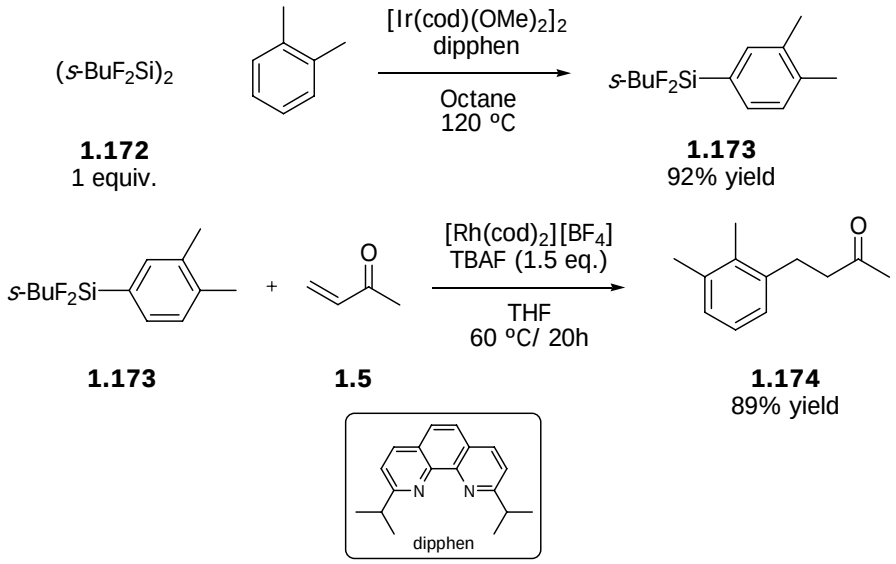
Scheme 44

Organosiloxanes have proved to be valuable precursors in the asymmetric conjugate-addition reaction.[133] Using the $[Rh(cod)(MeCN)_2][BF_4]$ catalyst with BINAP based ligands a range of both aryl and alkenyl siloxanes have been successfully coupled to cyclic and acyclic enones (**1.165-1.168**). Alkenyl siloxanes furnish the corresponding (*E*) or (*Z*)- isomer with no loss of selectivity (**1.169-1.171**). Other substrates such as esters and unprotected crotamides can also be utilised successfully. The reaction can be extended to utilise a tandem process utilising terminal alkynes and triethoxysiloxane giving the alkenyl siloxane reagent in the presence of a rhodium-BINAP catalyst system.[134] This rhodium-catalysed hydrosilylation, conjugate-addition procedure allows rapid access to a range of alkenylated products with high enantioselectivity and (*E*)-geometry (*Scheme 45*).



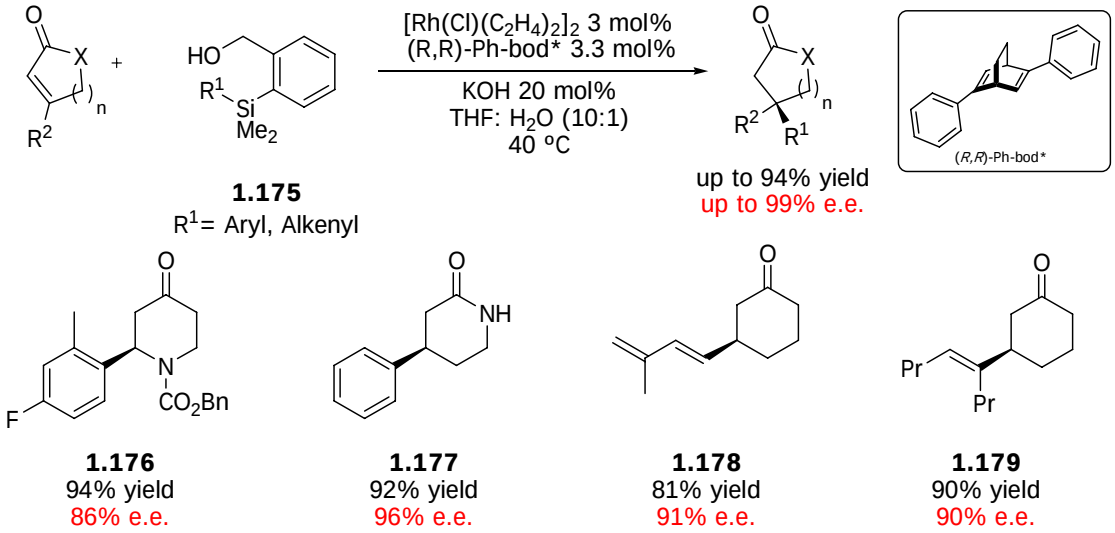
Scheme 45

Recently a number of alternatives to organosiloxanes have been published.[135, 136] Miyuara has proposed a direct C-H silylation of arenes with fluorodisilanes.[135] Similar reactions have been widely developed based on a similar strategy with C-H borylation of arenes.[137, 138] Using a suitable iridium-ligand species and 1,2-di-tert-butyl-1,1,2,2-tetrafluorodisilane (**1.172**) as the silylating agent, the corresponding silane species was formed with good yield and regioselectivity. The aryltrifluorosilanes obtained were able to undergo both palladium cross-coupling reactions and rhodium-conjugate addition reactions in high yields. The rhodium-conjugate addition occurred in the absence of water but required an external fluoride source such as tetrabutylammonium fluoride (TBAF) to turnover catalyst. The addition of *xylyl* trifluorosilane reagent (**1.173**) to MVK (**1.5**) gave the corresponding 4-(2,3-dimethyl phenyl)butan-2-one product (**1.174**) in 89% yield. Such coupling reagents show promise in metal-catalysed reactions although, large quantities of arene (10 eq.) were required to give complete consumption of the silylating agent (*Scheme 46*).



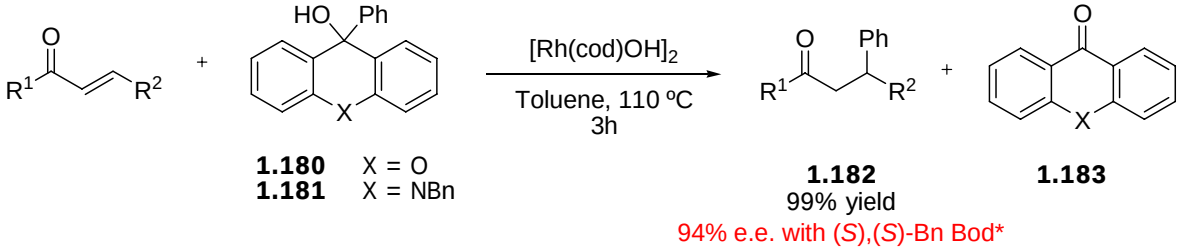
Scheme 46

Hayashi and co-workers have negated the need for such external fluoride sources with the synthesis of organo [2-(hydroxymethyl)phenyl]dimethylsilanes (**1.175**).[136] Such organometallics have been known recently for their smooth couplings with both palladium-catalysed Suzuki reactions[139] and allylation of aldehydes[140] but had never been used in rhodium-catalysed transformations. The reaction conditions are similar to previous boronic acid type additions with a rhodium dimer and (*R*),(*R*)-Ph-bod* ligand being used in a THF-water mixture. It was found that the silane reagent had to be added slowly and in a ratio of 3.5 eq. to substrate otherwise competing protonolysis leading to dimethylarylsilane was the major pathway. A range of substrates can be used including piperidones (**1.176**) and secondary amides (**1.177**) with good yields and enantiomeric excesses. The organometallic reagents are also excellent for alkenylation of cyclic substrates with dienes (**1.178**) and α-substituted alkenes (**1.179**) being incorporated readily (*Scheme 47*).



Scheme 47

A final novel organometallic has been presented by Hayashi *et al* through a β-hydrocarbonyl elimination process seen with transition-metal alkoxides.[141] Studying a range of α-α′-disubstituted benzylalcohols, only the reactions of xanthenol (**1.180**) and acridinol (**1.181**) gave yields of the desired arylated enone product (**1.182**) with the eliminated ketone side-product. Using acridinol based alcohols lead to a good range of functionality being incorporated into the final product. The reaction is rapid taking only 3 hours and the amounts of α, α-substituted benzylalcohol being only 1.1 equivalents, in addition to this combining the system with chiral diene ligand (*S*),(*S*)-Bn Bod* gives excellent selectivity with acyclic enones (*Scheme 48*).



Scheme 48

The proposed catalytic cycles involves the formation of a rhodium-alkoxide species formed by the benzylalcohol and rhodium-complex (**1.184**). This can in turn undergo β-hydrocarbonyl elimination giving the corresponding rhodium-aryl species (**1.185**) and the eliminated ketone byproduct (**1.183**). Subsequent insertion followed by hydrolysis of the rhodium oxa-π-allyl

species (**1.184**) with a catalytic amount of alcohol regenerates the active species and gives the desired product (**1.182**) (*Figure 11*).

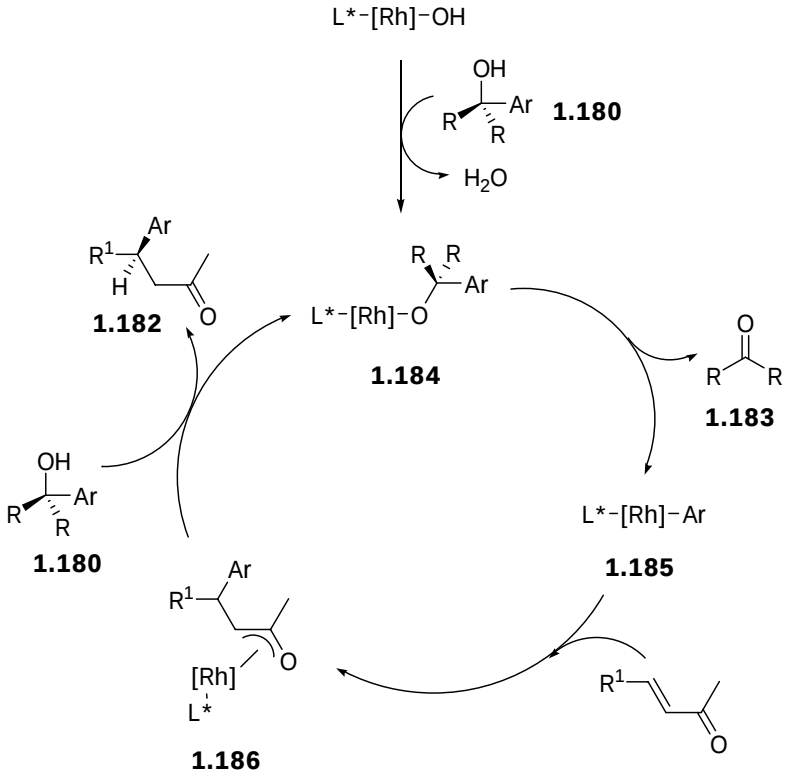


Figure 11

1.5 Detailed Mechanism of Reaction

Hayashi published the generally accepted mechanism for rhodium-catalysed 1,4-addition in 2002 with detailed studies on cyclic and acyclic activated alkenyl species.[31] The first step involves formation of the active rhodium-hydroxyl precursor (**1.187**) by loss of ligands such as acac or cod, the organometallic utilised can then undergo transmetallation with the metal centre (**1.185**). Excesses of boronic acid are employed as the active species is labile in the presence of water leading to the hydroxyl-rhodium species being reformed and the arene proto-deboronated product (**1.188**) being formed. This is the competing reaction pathway in such reactions and must be minimised in order to give good reaction yields. Introduction of the substrate leads to metal-alkene coordination (**1.189**) which allows subsequent aryl fragment insertion into the alkene with formation of a rhodium oxa-π-allyl species (**1.190**). Enatioselectivity of the product is controlled by the facial selectivity of the chiral phosphine

ligand. Finally hydrolysis of the rhodium-enolate by water in a racemic process gives the final product (**1.40**) and regenerates the catalytic cycle (*Figure 12*).

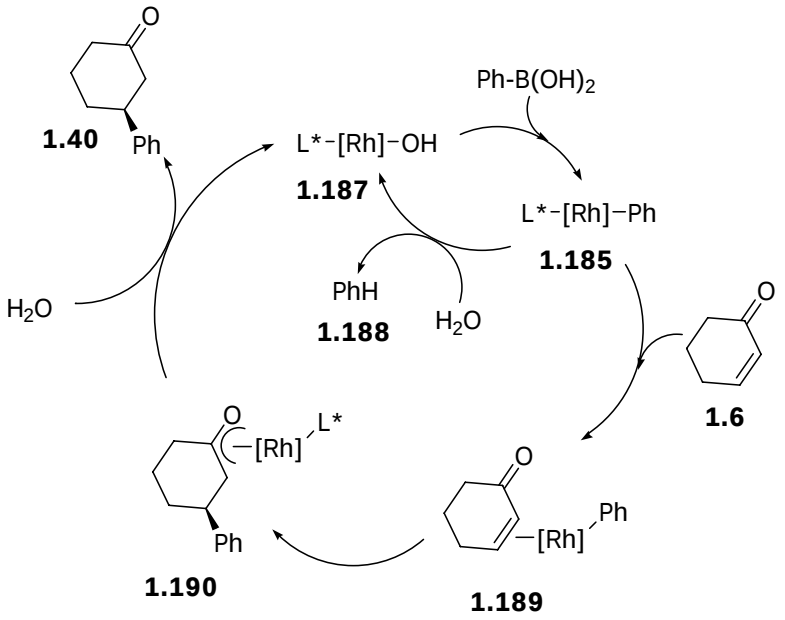
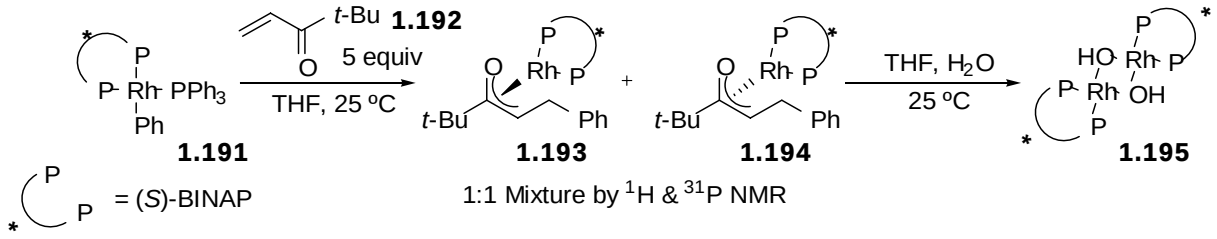


Figure 12

In order to ascertain the role of the oxa-π-allyl rhodium species, Hayashi undertook a series of detailed NMR experiments.[31] Synthesis of the triphenylphosphine aryl rhodium complex (**1.191**) was achieved from the $[RhCl(BINAP)]_2$ dimer by action of triphenylphosphine displacement followed by reaction with phenyl lithium. Using the complex, the reaction of *tert*-butyl vinyl ketone (**1.192**) at room temperature was followed by multinuclear NMR. The signals corresponding to the original triphenylphosphine aryl rhodium complex were gradually replaced with two new sets of signals assigned as diasteromeric rhodium oxa-π-allyl species (**1.193, 1.194**). These signals were compared with authentic samples of the potassium enolate of *tert*-butyl 2-phenylethyl ketone according to the procedures reported for the preparation of oxa-π-allylrhodium complexes from $[RhCl(PR_3)_2]_2$ and potassium enolates.[142, 143] Finally upon addition of water the new complexes were immediately converted generating a new rhodium dimer species (**1.195**) (*Scheme 49*).



Scheme 49

The selectivity exhibited can be explained by steric grounds based on a quadrant system often utilised in asymmetric hydrogenation procedures. Using (*S*)-BINAP as a chiral phosphine ligand the coordination of the enone is sterically encumbered on one face of the ring. This leads to selective formation of the rhodium-complex with *Si*-coordination of the cyclohexenone ring. Hydrolysis of this complex leads to optically pure arylated product (**1.40**) (*Figure 13*).

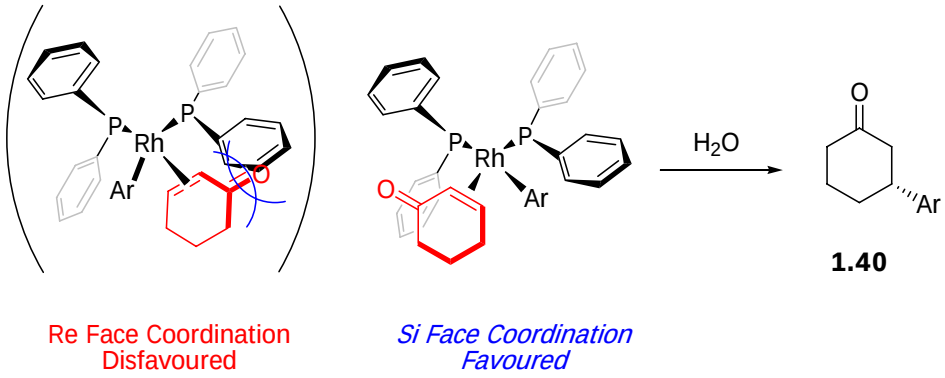


Figure 13

Chiral diene ligands occupy a less bulky configuration about the rhodium-complex which allows an explanation of the results observed with maleimide species previously discussed. When bisphosphines such as BINAP are utilised in the reaction, steric clashing of the R-group on the substrate with the binaphthyl ring system leads to an energetically unfavourable situation. Thus to minimise the repulsions aryl insertion occurs at the substituted position of the maleimide giving an all-carbon quaternary centre. However, using chiral diene ligands such as (*S*),(*S*)-Ph-Bod* the upward orientation of the phenyl substituent on the diene ligand significantly reduces the steric repulsion with the *R*- group on maleimide. As a result, the steric hindrance between the aryl group on the rhodium species and the R- group on maleimide becomes the dominant factor. This allows insertion to occur on the unsubstituted end of the alkene giving the corresponding *cis-trans* product (**1.115**) (*Figure 14*).

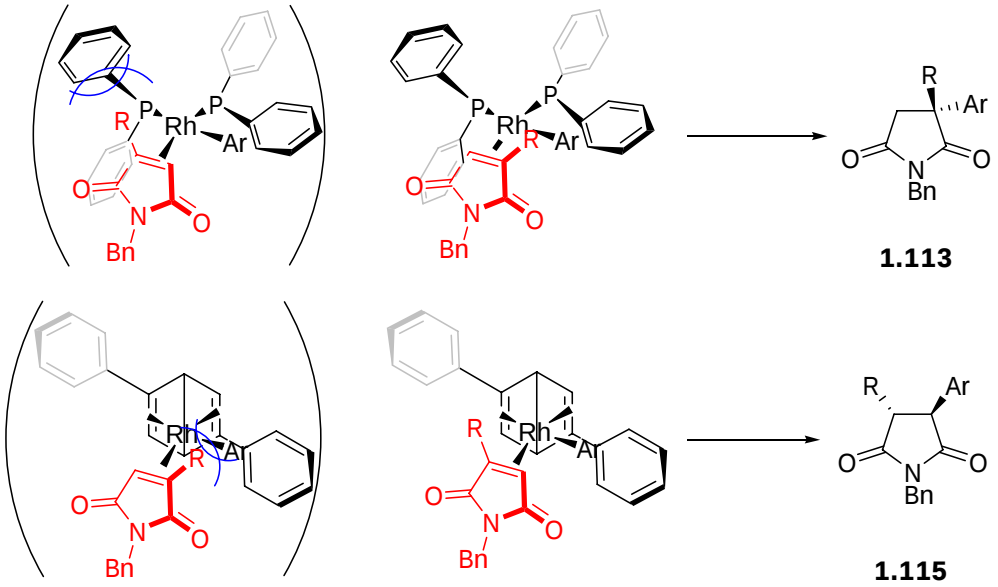


Figure 14

1.6 Summary

Rhodium-catalysed additions have improved markedly from initial reports in 1992; reactions may be performed with greater selectivity, at lower temperatures and with less coupling reagent than previously described. The major breakthrough in catalysis involving insertion of an aryl or alkenyl fragment is chiral-diene ligand systems. These give vastly improved reactivity and are highly consistent in the enantioselectivity obtained regardless of substrate choice and steric and electronic factors of the organometallic reagent.

The major challenge currently is in rhodium-catalysed tandem processes, where rhodium successfully catalyses more than one reaction. Using such reaction systems will lead to synthesis of structurally complex molecules with a number of carbon or heteroatom bonds formed with complete control of selectivity.

1.7 References

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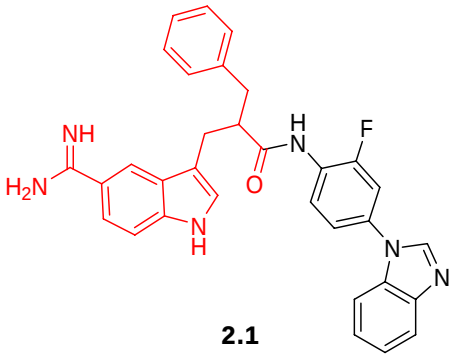
Chapter 2 – Synthesis of α,α′-Dibenzyl Esters *via* Tandem Rhodium-Catalysed Enolate Protonation

2.1 Aims and Objectives

The aim of this chapter is to explore the addition of aryl potassium trifluoroborate salts to a novel range of aromatic and heterocyclic α-substituted acrylate esters. Such compounds are versatile synthetic intermediates in a range of natural and medicinal products such as 5-amidinoindoles (**2.1**) used in the treatment of deep vein thrombosis (*Figure 1*).[1]



2.1

Figure 1

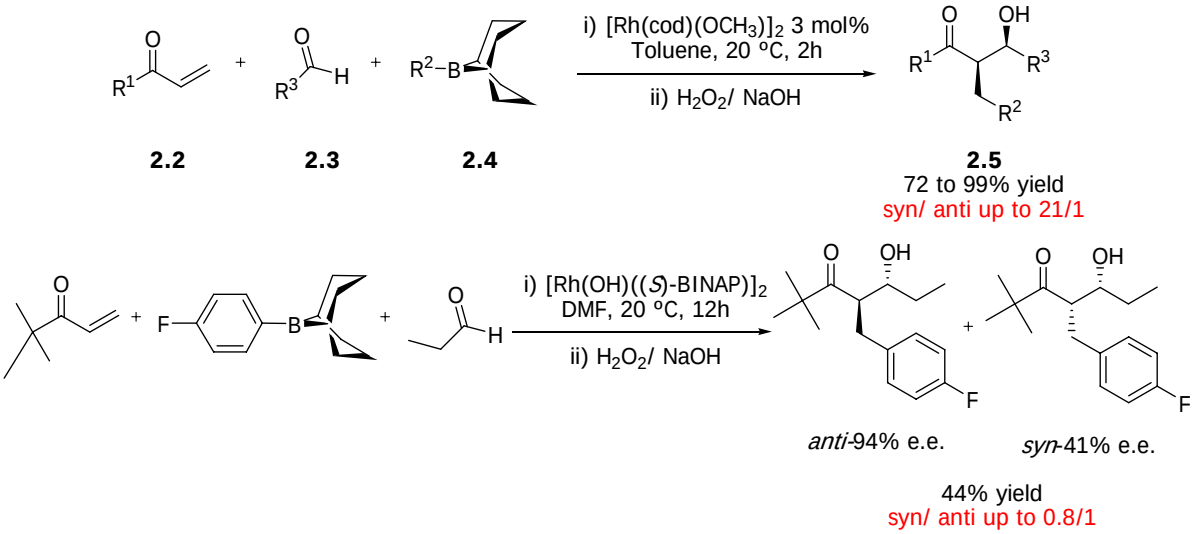
Initial studies in this chapter involve the scope and reaction of 5-alkyl substituted derivatives of Meldrum's acid with a range of alcohols to give a number of novel structures. These compounds are quick to assemble and give a large amount of functional group complexity, previously unseen in other unsaturated ester substrates. Once this has been achieved the key reaction parameters of racemic and asymmetric rhodium-catalysed enolate protonation will be developed. By matching of a variety of rhodium salts, enantiopure ligands, organoboranes and additives, we hope to generate of chiral α-α′ dibenzylated esters.

2.2 Rhodium-Catalysed Tandem Reactions

In Chapter 1 it was shown that the oxa-π-allylrhodium intermediate plays a key role when determining enantioselectivity in conjugate-addition reactions.[2, 3] There has been interest in using this rhodium-enolate by trapping the species with a suitable reagent to give other metal or silyl enolate species. By forming a suitable intermediate with boron, silicon, titanium or

zinc, electrophiles could be added providing further synthetic complexity in a single reaction vessel. In addition, if arylation can be achieved in high selectivity it is possible to influence neighbouring stereocentres yielding well resolved chiral molecules. The major areas at present are in the areas of addition-aldolisation, cyclisation and asymmetric protonation, these areas will be discussed subsequently.[4]

In 2002 Hayashi presented the first example of a rhodium-catalysed tandem reaction based on a oxa-π-allylrhodium intermediate.[5] Taking an unsaturated ketone (**2.2**), aliphatic aldehyde (**2.3**) using 9-aryl-9-borabicyclo-[3.3.1] nonanes (**2.4**) (B-Ar-9-BBN) as the organoboron reagent and $[Rh(cod)(OCH_3)]_2$ as the catalyst under anhydrous reaction conditions, a tandem 1,4-addition-aldol reaction could be achieved giving products (**2.5**) with high *syn-anti* selectivity. An asymmetric variant of the reaction can also be realised using a preformed rhodium-BINAP catalyst, giving the *anti*-product in 94% enantiomeric excess. The formation of the enantiomerically enriched products is important as it removes the boron enolate intermediate in the reaction, such a species would yield racemic aldol products (*Scheme 1*).



Scheme 1

The proposed mechanism for the racemic process proceeds *via* the formation of a rhodium-aryl species as previously discussed.[3] This inserts across the double bond of the enone leading to the oxa-π-allylrhodium intermediate (**2.6**) which is trapped as the 9-BBN enolate (**2.7**). Aldolisation can then occur with an appropriate aldehyde species (**2.8**). Hydrolysis gives the desired aldol product in high selectivity (*Figure 2*).

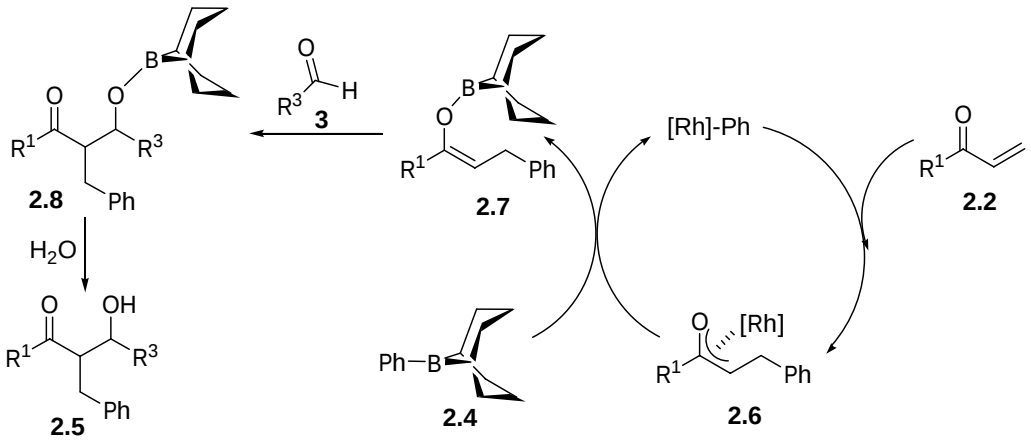
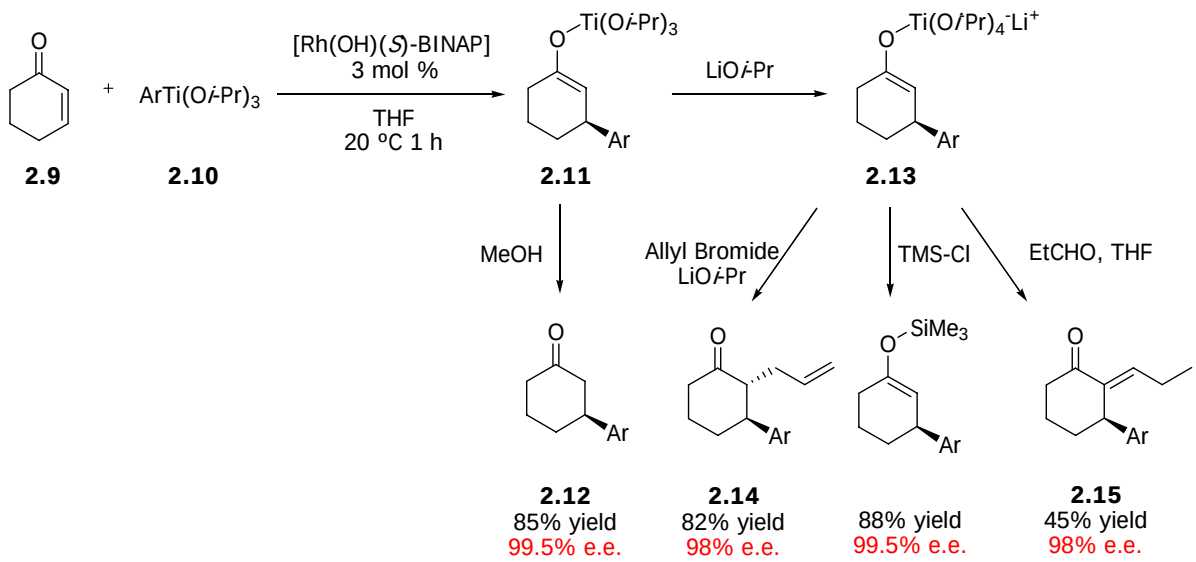


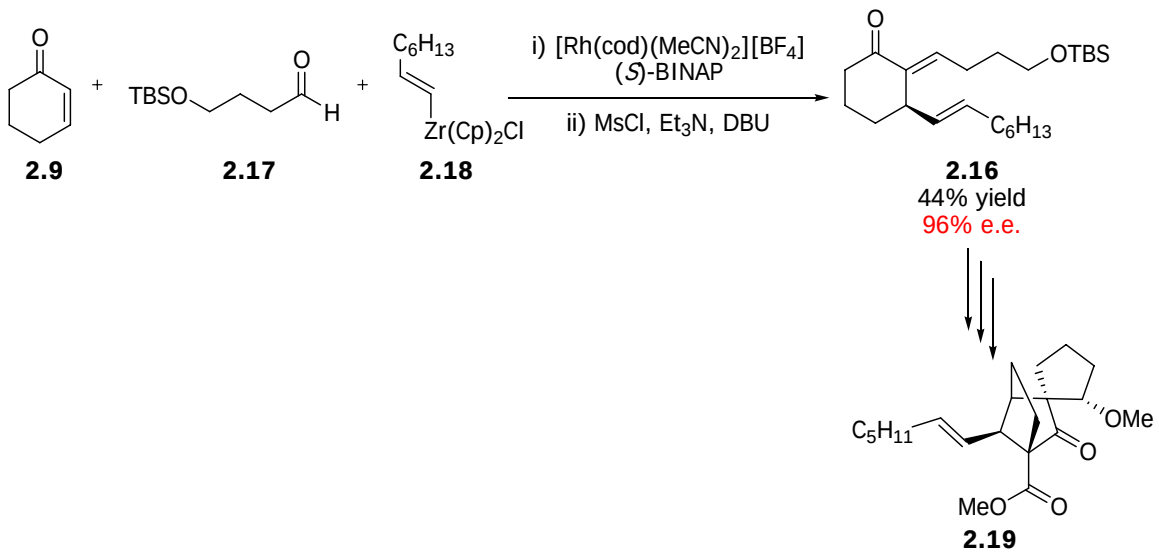
Figure 2

The trapping of rhodium enolates with cyclic enones such as 2-cyclohexenone (**2.9**) has also been achieved and early reports show the use of aryl titanium species (**2.10**) as suitable arylation-enolate forming reagents.[6] Using a preformed rhodium-BINAP catalyst, synthesis of the aryl titanium enolate species (**2.11**) occurs at 20 ºC in anhydrous conditions. Hydrolysis of the enolate leads to the corresponding 3-subsituted cyclohexanone derivative (**2.12**) with high selectivity. In order to allow tandem transformations to occur the titanium species must be reacted with a further equivalent of lithium isopropoxide giving the tetra-valent titanate (**2.13**). Through this reactive intermediate α-alkylation occurs readily with allyl bromide giving two stereocentres in excellent diastereoselectivity (**2.14**). Aldol reactions with the corresponding alkyl aldehydes also occur giving the condensed alkenyl species (**2.15**) in moderate yields (*Scheme 2*). Analogous processes can be achieved with the 9-BBN boron species giving similar products with high yields and excellent selectivity.[7]



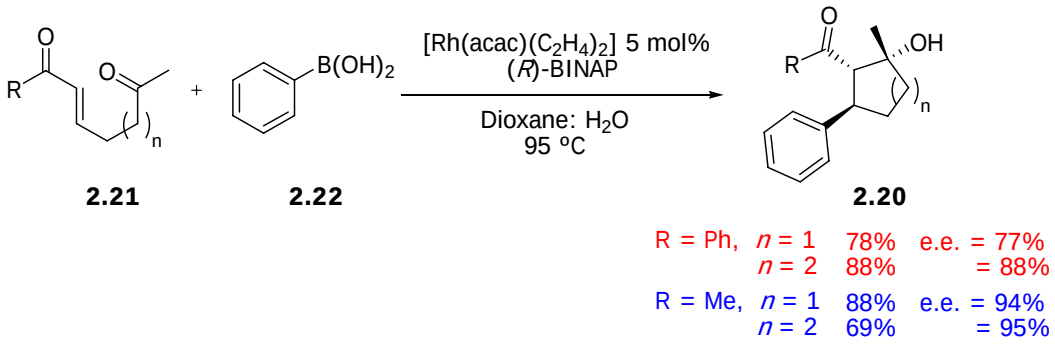
Scheme 2

This methodology has recently been applied in natural product synthesis by Nicolau and co-workers.[8] The group uses the *in situ* formation of an alkenyl zirconium species and rhodium-catalysed conjugate addition in the core motif of Vannusal A (**2.16**). Highly functionalised products are formed with good enantiomeric excesses starting from a mixture of 2-cyclohexenone (**2.9**), 4-(tributylsilyloxy) butanal (**2.17**) and an alkenyl cyclohexyl zirconium organometallic reagent (**2.18**). Using a cationic rhodium-BINAP complex a number of analogues can be formed rapidly with complete control of stereochemistry. This is an elegant and effective route towards the spiro-core (**2.19**) of the natural product carried out in a single reaction vessel (*Scheme 3*).



Scheme 3

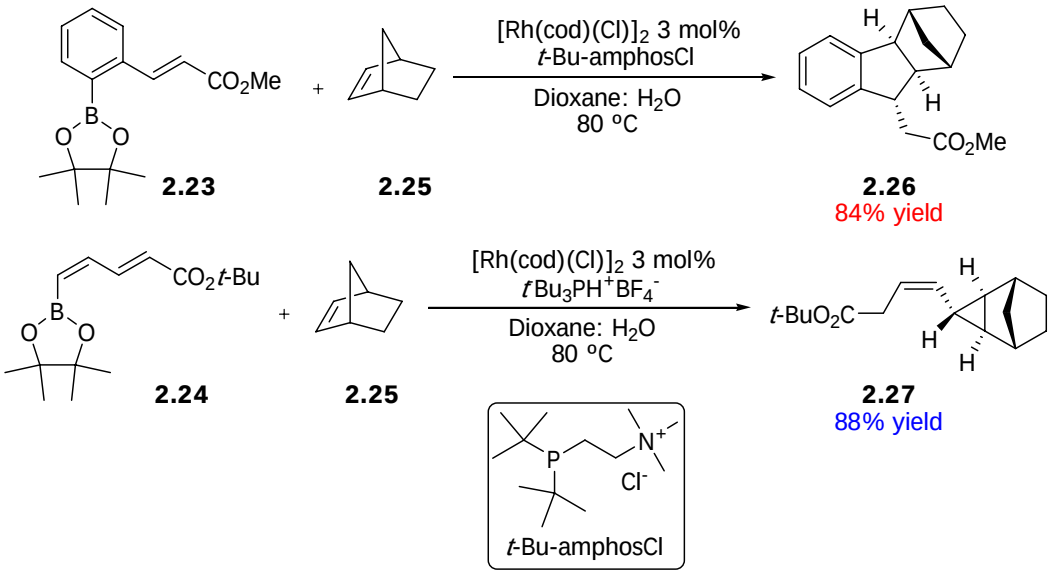
Rhodium-catalysed conjugate addition of an organometallic reagent can also be undertaken with internal electrophiles to give cyclised products. The use of rhodium in eneyne type cyclisations is well documented; however, many compounds are limited by substrate choice.[9] Krische and co-workers have described a catalytic tandem conjugate addition-aldol cyclisation.[10, 11] This methodology enables the formation of five- and six-membered ring products (**2.20**) from aromatic and aliphatic mono-enone mono-ketone precursors (**2.21**) with aryl boronic acids (**2.22**). The reaction occurs in a single vessel and the products formed contain three contiguous stereogenic centres created with high levels of relative and absolute stereochemical control (*Scheme 4*).



Scheme 4

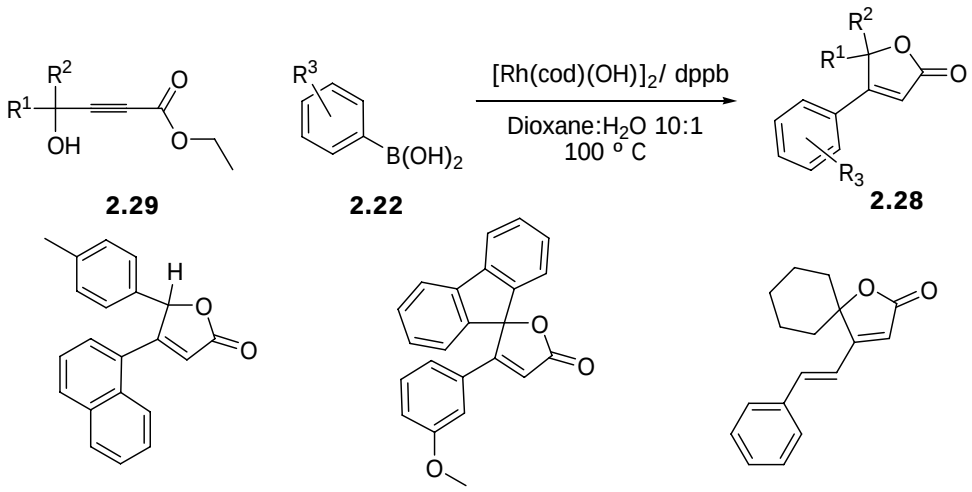
Lautens has reported a rhodium-catalysed tandem carbocyclisation of aryl boronate esters bearing a Michael acceptor and a strained alkene or alkyne tether point.[12, 13] Using a

rhodium-catalyst with a water soluble ligand such as *t*-butyl-AMPHOS the group has designed an alkenyl boronate (**2.23-2.24**) system which can readily react with alkenes, but is strained so that cyclisation occurs more readily than hydrolysis of the active rhodium species. Using an unactivated alkene such as norbornene (**2.25**) leads to a cyclised product (**2.26**) formed in greater than 20:1 diastereomeric excess. By varying the substrate and ligand a novel cyclopropanation product (**2.27**) can be observed, arising from rhodium-catalysed 1,6-addition of the organoboronate species (*Scheme 5*).[14]



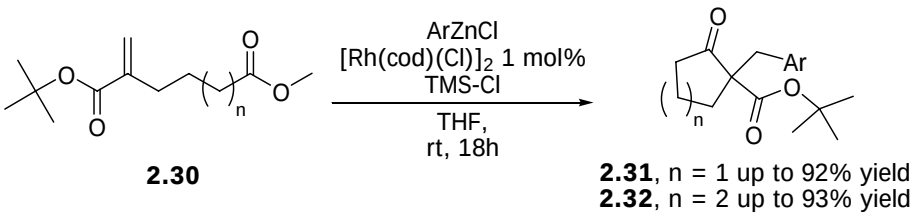
Scheme 5

Arcadi and co-workers have recently presented a method of forming 2(5*H*)-furanone compounds (**2.28**) involving a tandem rhodium-catalysed addition-lactonisation cascade.[15] The reaction involves the rhodium-catalysed addition of aryl boronic acids (**2.22**) to alkynes which allows for high regio and stereoselectivity. A $[Rh(cod)(OH)]_2$ system with dppb as the ligand gave the desired tandem reaction without any undesired side products such as homocoupling. The rhodium-catalysed reaction of alkyl 4-hydroxy-2-alkynoates (**2.29**) bearing a tertiary propargylic alcohol group resulted in reversal of the regioselectivity compared to that observed in the palladium-catalysed process. In addition to this the steric bulk about the triple bond does not affect reactivity (*Scheme 6*).



Scheme 6

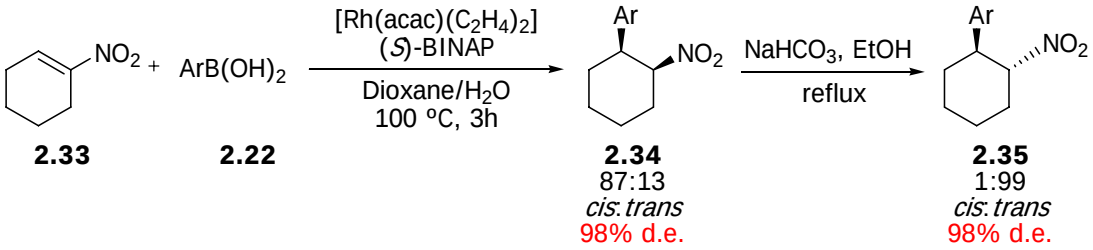
Using arylzinc halide reagents can also lead to rhodium-catalysed addition cyclisation.[16] Using a 1,1′-alkenyl ester substrate such as dimethyl itaconate (**2.30**) with a rhodium catalyst and aryl zinc chloride leads to formation of the cyclopentanone product (**2.31**) *via* a consecutive 1,4 addition cyclisation process. The addition of trimethylsilyl chloride (TMS-Cl) was critical in formation of the cyclopentanone (**2.31**) or cyclohexanone (**2.32**) products over 1,4-addition hydrolysis side-products. The reaction occurs under very mild conditions with low catalyst loadings and is tolerant of a range of substituted esters at the acrylate end of the molecule. Kinetic studies show that the reaction is also extremely rapid with greater than 70% product conversion observed in 7 minutes by NMR experiments (*Scheme 7*).



Scheme 7

Rhodium-catalysed conjugate additions give highly selective additions due to the chiral environment of the metal-ligand species; however, the situation can be complicated further when the protonolysis occurs to form the new chiral centre. Such tandem 1,4-addition protonation reactions were first observed by Hayashi *et al* in the conjugate addition of arylboronic acids (**2.22**) to α-substituted nitroalkenes.[17] Arylboronic acid (5 eq.) reacts with

1-nitrocyclohexene (**2.33**) in the presence of [Rh(acac)(C_2H_4)$_2$]/(S)-BINAP catalyst at 100 °C for 3 hours in dioxane-water (10:1) to give the *cis*-isomer (**2.34**) in 89% yield. Both the *cis* and *trans* diastereoisomers were optically pure (98% e.e.) but appeared in an 87:13 *cis:trans* ratio. This can be explained by the slow interconversion of the *cis*-isomer into the more stable *trans* analogue (**2.35**). By refluxing in the presence of sodium carbonate, the more thermodynamically favourable *trans*-isomer can be formed exclusively with no loss of enantioselectivity (*Scheme 8*).



Scheme 8

A plausible mechanism can be envisaged by using knowledge of other α,β-unsaturated systems, with coordination of rhodium-aryl species followed by insertion of the phenyl ring. The same stereochemical model can be used to show that the aryl group will be in the (*S*)-configuration if (*S*)-BINAP is used, as the nitro group will occupy the vacant lower quadrant of the catalyst. Another stereocentre is formed during the hydrolysis step, with equatorial protonation favoured due to approach from the less hindered face yielding the *cis* product. The ability to form the *trans* product by refluxing the *cis* material in base shows that the first stereocentre formed is fixed by the preceding reaction (*Figure 3*).

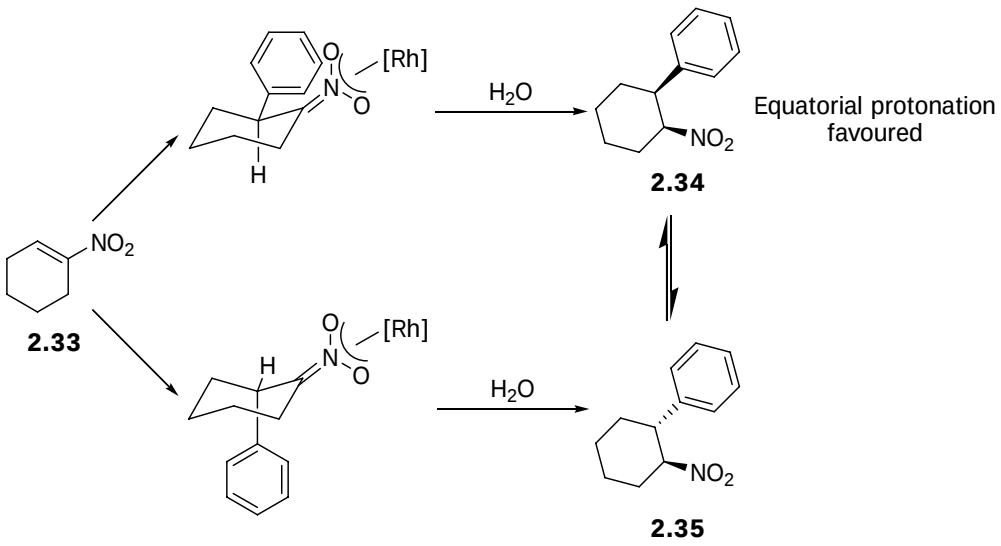
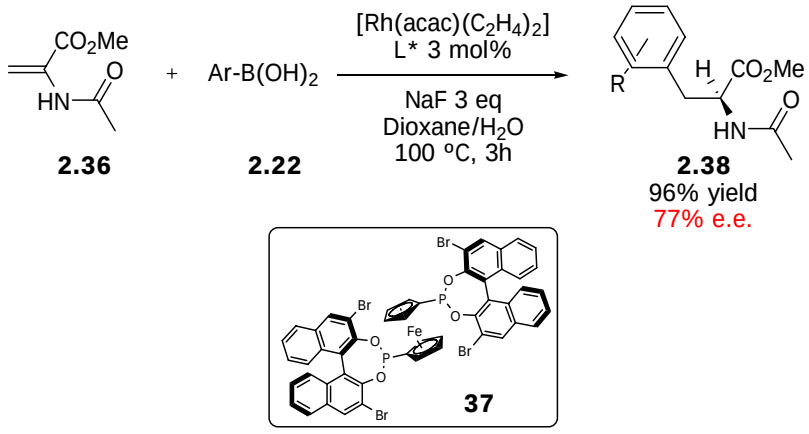


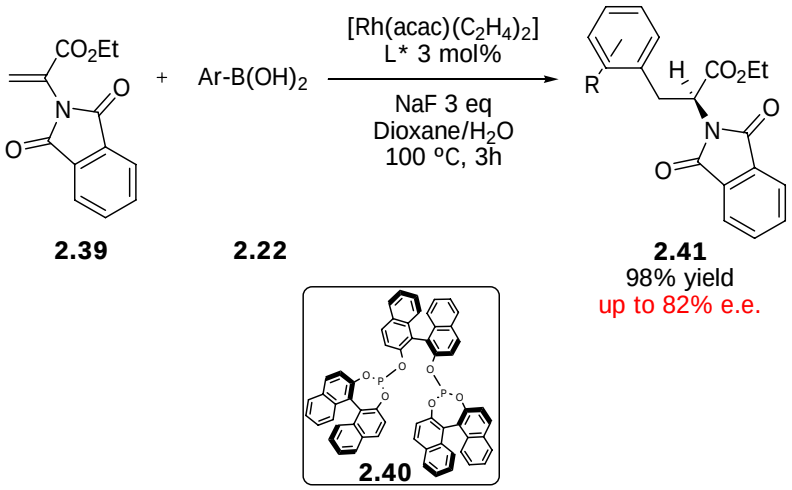
Figure 3

Rhodium-catalysed enolate protonation gives an accessible route to the synthesis of α and β-amino acids. The reaction has been attempted by numerous groups employing organostannane,[18] organosilicon,[19] and organobismuth[18] with no enantioselectivity reported. The first example of an asymmetric rhodium-catalysed enolate protonation was briefly described by Reetz, in the 1,4-addition of substituted phenylboronic acids (**2.22**) to α-acetamido acrylic acid esters (**2.36**) using chiral BINOL-based diphosphonites (**2.37**) as ligands.[20] The reaction occurs in quantitative conversion to product (**2.38**) but enantioselectivity is modest at 71% e.e. This can be improved to 77% e.e. with the addition of 3 eq. of sodium fluoride although this is not well explained (Scheme 9).



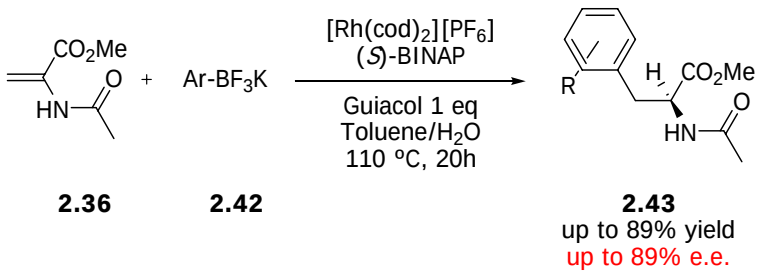
Scheme 9

This methodology was expanded upon by Frost and co-workers who had previously reported the synthesis of amino acids under aqueous conditions.[21] Using ethyl α-phthalimidoacrylate (**2.39**) and a chiral rhodium-complex containing an enantiopure diphosphite ligand (**2.40**) a range of substituted phenylalanine α-amino acids (**2.41**) could be formed rapidly and in good enantiomeric excess.[22] The reactions were tolerant to electron rich and electron deficient substitution on the phenyl ring, and could readily tolerate sterically bulky aryl fragments such as 1-naphthalene boronic acid (Scheme 10).



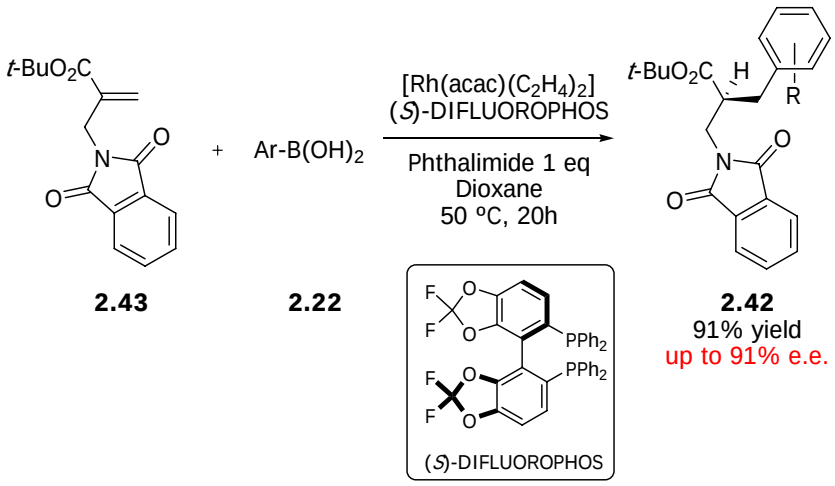
Scheme 10

Enolate protonation to this point had been studied in a similar manner to previous 1,4-addition reactions. Genet and co-workers discovered that changing the proton source in the reaction, for example using achiral phenol derivatives in place of water, could dramatically improve reproducibility and selectivity.[23] Using potassium trifluoroborates (**2.42**) as coupling partners in conjunction with guiacol (2-methoxyphenol) as a proton source a range of aryl, alkenyl and heteroaryl phenylalanine derivatives (**2.43**) could be synthesised in high yields and enantioselectivity (Scheme 11).



Scheme 11

Recently Sibi has utilised enolate protonation in synthesis of protected β-amino acids (**2.42**) using rhodium-catalysed processes.[24] This methodology is complementary to other amino acid syntheses using Lewis acid catalysed routes with magnesium catalysis, as it allows aryl incorporation into β-phthalimidoacrylate substrates.[25] A racemic process to give protected β-phenylalanine derivatives has been previously described[26] but until this time no asymmetric process had been achieved. By optimisation of rhodium-ligand combinations and proton source, it was found that DIFLUORPHOS ligand and phthalimide an achiral imide gave the best results and selectivity. Two major improvements were noted, the first was that using *tert*-butyl β-phthalimidoacrylate (**2.43**) is essential for obtaining high selectivity, with the less bulky methyl ester compound giving no selectivity. Secondly a strong correlation between the level of enantioselectivity and the nature of the proton donor was observed. The group postulates that phthalimide carbonyl groups can coordinate to the rhodium leaving the NH *ortho* to the substrate giving enantioenriched materials in a similar manner to *ortho* substituted phenols (*Scheme 12*).

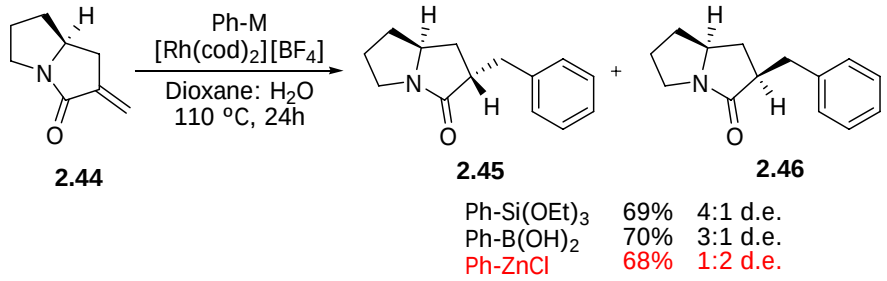


2.43 **2.22** **2.42**
91% yield
up to 91% e.e.

Scheme 12

Using amino acids as starting materials has led to some interesting products incorporating 1,4-addition enolate protonation methodology. Hargrave *et al* have undertaken the asymmetric synthesis of 2-substituted pyrrolizidinones using such routes.[27] The synthesis starts from commercially available *N*-Boc-L-proline and *via* a 5-step chemical synthesis gives the cyclic α-dehydro-γ-amino acid (**2.44**) suitable for rhodium-catalysed transformations. By taking advantage of the chiral environment formed by the cyclised proline lactam a range of organometallic reagents were screened to determine the highest diastereomeric excess. It was

found that organosiloxanes and boronic acids give diasteroisomer (**2.45**) in a 4:1 diasteromeric excess. More surprisingly switching to more reactive aryl zinc species gives the opposite isomer (**2.46**) in a 2:1 d.e. (*Scheme 13*).



Scheme 13

The mechanism can be explained by the rate of transmetallation, which dictates facial selectivity and thus the subsequent mode of protonation. Using organoboronic acids or siloxanes leads to a rhodium oxa-π-allyl species which is predominantly formed on the convex face of the molecule (**2.47**). Subsequent protonation of this active species then arises by prior coordination of water to rhodium leading to product (**2.45**). In contrast using arylzinc chloride species the transmetallation step is fast, occurring at room temperature leading to regeneration of the arylrhodium species with conversion of the oxa-π-allyl species to the zinc enolate (**2.48**). On quenching this reaction with water, protonation occurs preferentially at the less hindered convex face resulting in the formation of (**2.46**) (*Figure 4*).

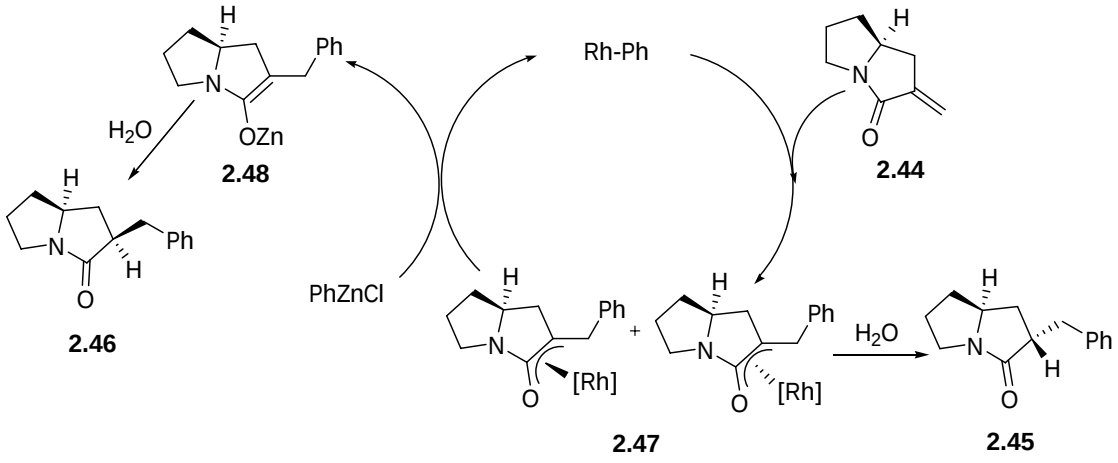
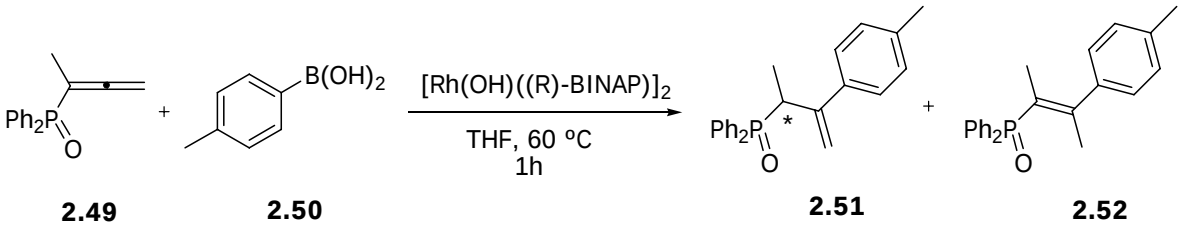


Figure 4

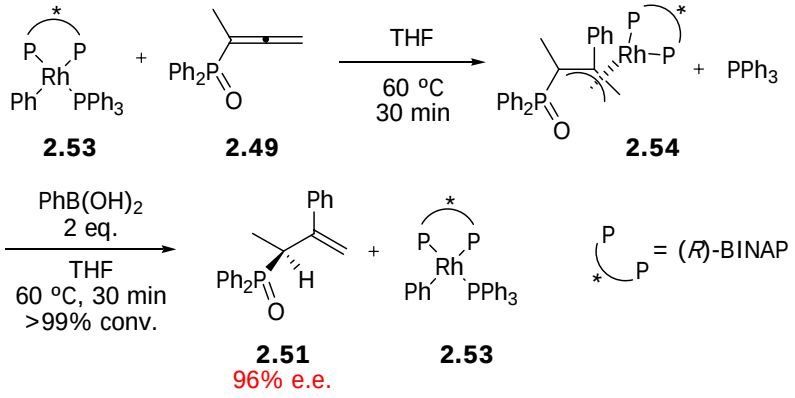
Hayashi has attempted rhodium-catalysed addition enolate protonation with phosphinylallenes (**2.49**), which are highly stable crystalline allene species.[28] By using a preformed rhodium-

BINAP complex in conjunction with 4-tolyl boronic acid (**2.50**), the 3-(diphenylphosphinyl)-3-methyl-1,2-butadiene substrate was converted into the corresponding hydroarylation product (**2.51**) with 89% e.e. together with a considerable amount of the achiral conjugated by-product (**2.52**). By switching the solvent system and repeating the reaction at lower temperature, the chiral product could be obtained almost exclusively in 97% e.e. (*Scheme 14*).



Scheme 14

In the same publication the only mechanistic insight into enolate protonation is discussed. The 3-(diphenylphosphinyl)-3-methyl-1,2-butadiene substrate was reacted with stoichiometric quantities of rhodium catalyst. Treatment of the highly reactive aryl-rhodium complex (**2.53**) with phenyl boronic acid (1 eq.) in THF-d_8 at 60 °C for 30 min brought about selective formation of a new rhodium complex (**2.54**), and a residual triphenylphosphine peak by ^{31}P NMR. The oxa-π-allylrhodium intermediate can be successfully isolated and crystallographic data was collected showing the rhodium in a square planar configuration with the absolute configuration of the π-allyl moiety is 2*R*, 3*R*. Upon addition of phenyl boronic acid solution in THF-d_8 the phenylated product has the same absolute stereochemistry as the *S*-isomer. This implies that the protonation in the catalytic system occurs after the equilibration into a thermodynamically stable oxa-π-allylrhodium intermediate and the *R*-configuration of the π-allyl complex suggests that protonation occurs from the same face as the coordinated rhodium species (*Scheme 15*).



Scheme 15

Tandem processes involving a metal-catalysed addition of an organometallic reagent and trapping with a suitable external or internal reagent is still a relatively unexplored area of asymmetric catalysis. Only the publications outlined above show the use of a rhodium-catalysed conjugate addition enolate protonation strategy as the key step in forming chiral molecules. Considering the small number of publications it is still to be expanded upon with new substrates and catalyst systems.

2.3 Results and Discussion - Initial Studies with Acrylate Esters

Work within the group has previously made use of commercially available substrates such as dehydroamino acids and dimethyl itaconate with structural complexity incorporated by the addition of the aryl or alkenyl organometallic reagent. This has led to lower yields with a number of heteroaromatic and 2-substituted boronic acids due to protodeboration of the coupling partner. Finding a synthetic route to aromatic acrylate ester derivatives, should alleviate this problem by intergrating such functional groups into the starting material. This in turn allows an organometallic reagent that is less prone to protodeboronation to be added enantioselectively setting up an α,α'-dibenzyl ester motif. The desired synthetic route arises from the use of Meldrum's acid and the facile Knoevenagel condensation that occurs with aldehydes, or coupling with carboxylic acids (**2.55, 2.56**). The formed alkylidene malonate (**2.57**) species can undergo conjugate reduction to give the benzyl alkylidine malonate (**2.58**). Subsequent methylenation leads to the dehydrobenzylacrylate ester derivative (**2.59**) ideal for tandem rhodium-catalysed arylation protonation methodology (**2.60**) (*Figure 5*).

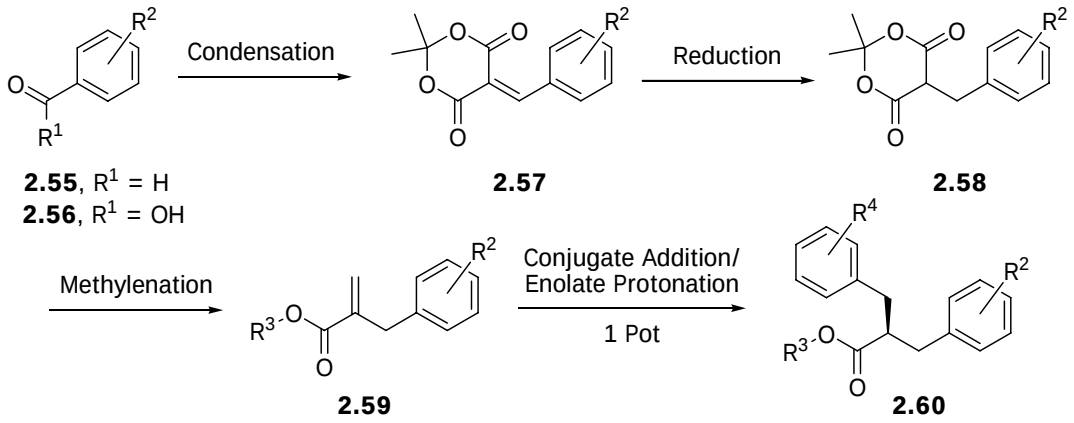
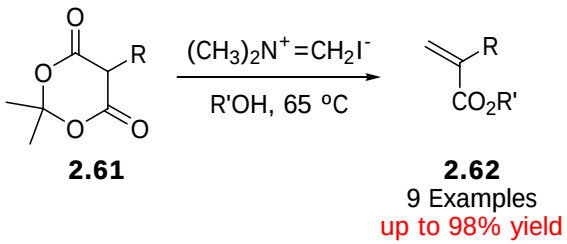


Figure 5

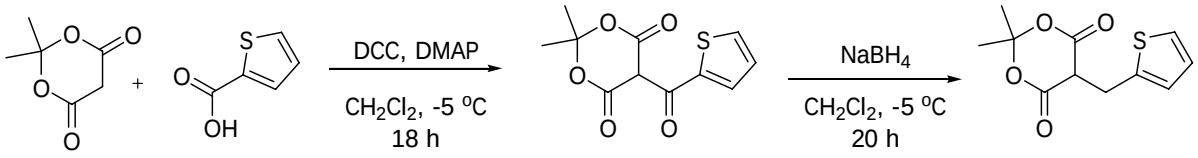
Initial studies were based on the reactions of Hin and co-workers in the synthesis of α-substituted acrylate esters.[29] A small range of alkyl, aryl carboxylic acids, as well as *N*-Boc protected amino acids were reacted in a one pot process to form the corresponding 5-monosubstituted Meldrum's acid derivative (**2.61**). These compounds were then subjected to a range of Mannich reaction conditions to give the formation of the dimethylamino derivative, which is eliminated under refluxing alcoholic conditions to give the desired acrylate ester product (**2.62**). The reaction conditions are mild and tolerate many functional groups commonly used in organic synthesis. An added advantage is this process tolerates sensitive functional groups such as *S*-triphenylmethyl thioether, *tert*-butyl carbamate, and benzyl and *tert*-butyl esters (*Scheme 16*).



Scheme 16

The reaction appeared to be an effective route to acrylate substrates of interest, with scope to use a range of aryl carboxylic acids in the reaction, with original reports only showing one such compound in 95% yield. To this end Meldrum's acid (**2.63**), 2-thiophene carboxylic acid (**2.64**) and DMAP were dissolved in anhydrous dichloromethane to give a white suspension to which DCC was added portion-wise at 0 °C over 1 hour. This allows coupling of the Meldrum's acid to the carboxylic acid. After leaving the reaction mixture overnight, the

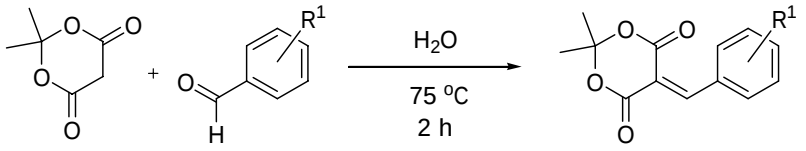
dicyclohexyl urea by-product was filtered and the reaction was cooled again to 0 °C. Acetic acid was then added to the crude 2,2-dimethyl-5-(thiophene-5-carbonyl)-1,3-dioxane-4,6-dione (**2.65**) and sodium borohydride was added over a one hour period. Upon leaving at 0 °C overnight the product was extracted and dried to give a brown solid with the expected alkylidine malonate (**2.66**) observed in 45% conversion by ^{1}H NMR. Unfortunately the reaction mixture was complex giving difficulty in isolating a quantitative amount of pure product for further use. In addition, the reaction was time-consuming (over 2 nights) and required a significant amount of work-up to isolate the impure mixture at each step (*Scheme 17*).



2.63 **2.64** **2.65** not isolated **2.66**

Scheme 17

In order to form a large array of substituted acrylate esters a different synthetic strategy was required. A range of routes to arylidine malonates have been described previously. Methods using strong base and DMF as a solvent,[30] neat aldehyde,[31] zinc dust,[32] and more recently pyridinium acetate[33] have all been used successfully in good to excellent yields. Bigi and co-workers have shown that water is an excellent medium for yielding the Knoevenagel condensation product (**2.67**) from the reaction of the corresponding aldehyde (**2.55**) and Meldrum's acid (**2.63**) (*Scheme 18*).[34, 35] This product could be cleanly isolated and then reduced via the reductive methodology suggested by Hin.[36] It was decided to attempt the aqueous Knoevenagel condensation method to yield the corresponding arylidine malonate, followed by conjugate reduction to give the required alkylidine malonate.

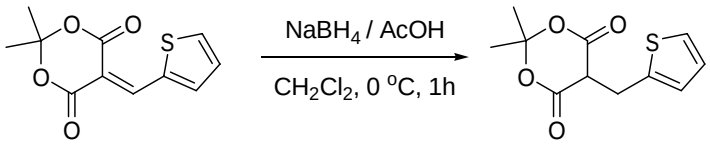


2.63 **2.55** **2.67** 8 Examples up to 94% yield

Scheme 18

Addition of Meldrum's acid (**2.63**) to a 2-thiophene carboxaldehyde (**2.68**) in water in an air atmosphere gave a vividly coloured solid condensation product after 2 hours at 75 °C. The compound was isolated *via* simple filtration and washed with water and hexane to give the desired arylidine malonate (**2.69**). The crude arylidine malonates could be used without further purification due to removal of liquid aldehydes by filtration. When using solid aldehydes with poor solubility in water, recrystallisation from hot ethanol or ethyl acetate removed residual aldehyde starting material. The products isolated were air and moisture stable making them ideal for large scale synthesis. Only a small number of aldehydes had been condensed in the original communication, thus it was gratifying to discover a wider range could be successfully employed. There was little difference in yield between electron rich and electron deficient functionalised aldehydes in the reaction. The ability to condense *ortho* functionalised aromatic aldehydes was seen as a positive result due to previous difficulties in 1,4-addition of 2- substituted boronic acids.

The next step in the synthesis is the conjugate reduction of the Michael acceptor using sodium borohydride in dichloromethane. 2,2-dimethyl-5-(thiophen-2-ylmethylene)-1,3-dioxane-4,6-dione (**2.69**) was cooled to 0 °C and dissolved in dichloromethane and acetic acid was introduced. After allowing the reaction mixture to stir for 15 minutes, sodium borohydride was added in small portions over one hour. In most cases a rapid colour change occurred in 15 minutes corresponding to the loss in conjugation and completion of reaction. All reactions occurred smoothly and in high yields with only an aqueous work-up required to give the alkylidine malonate products (**2.66**) (*Scheme* 19).

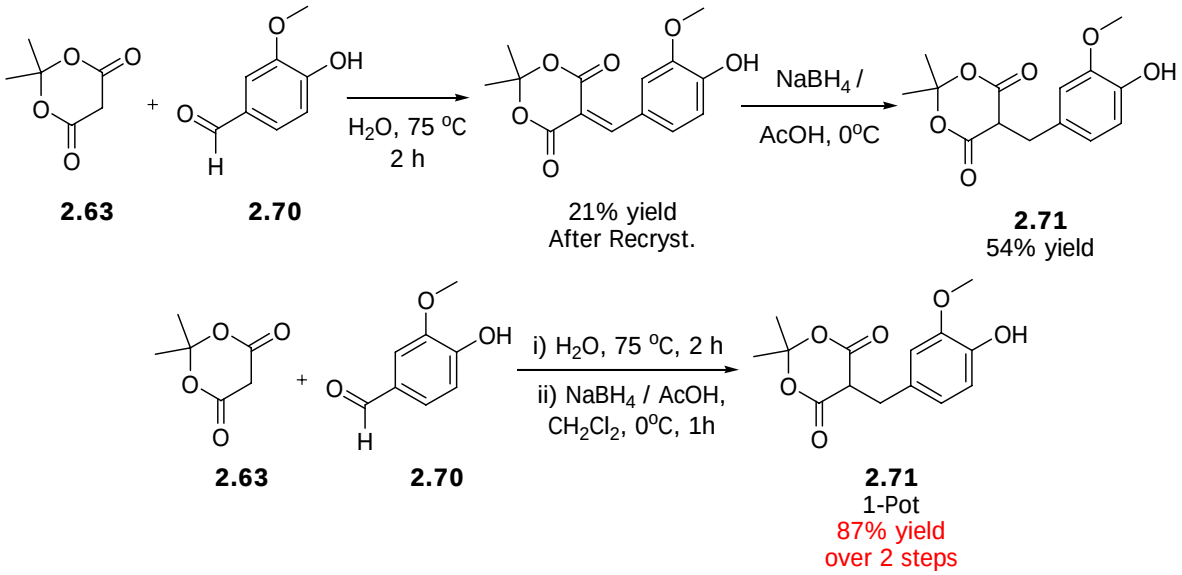


2.69 **2.66**
97% yield

Scheme 19

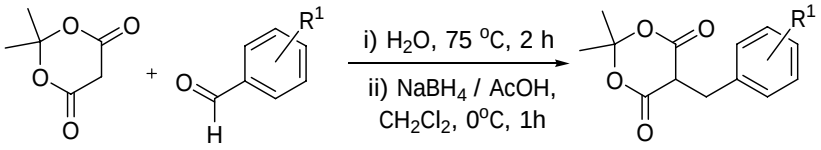
The majority of products could be isolated and reacted as separate starting materials; however, a number of the compounds were not easily isolated and tended to be gums or oils. This was rectified by undertaking the reaction to form the 5-monosubsituted Meldrum's acid derivatives in a single operation. Extraction of the product with dichloromethane and drying over

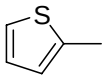
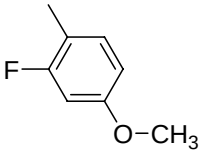
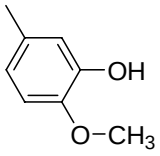
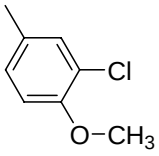
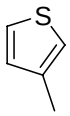
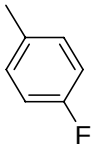
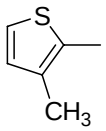
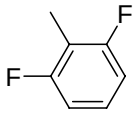
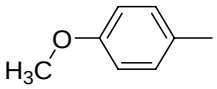
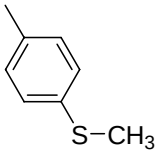
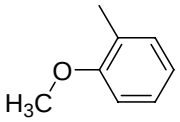
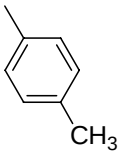
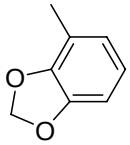
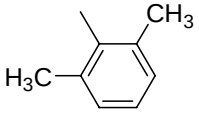
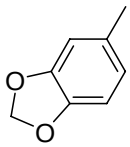
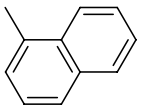
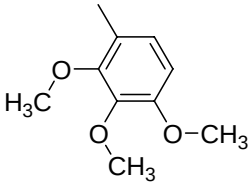
magnesium sulfate gave a crude solution of arylidine malonate that could be subsequently cooled to 0 °C for the conjugate reduction step. Adding sodium borohydride and acetic acid led to the same product as the 2 step method. The yields are similar and give improvements especially for oils such as the monosubstituted derivative based on vanillin (**2.70**), with excellent yields and pure alkylidine material (**2.71**) obtained after a single recrystalisation from hot ethyl acetate (*Scheme 20*).



Scheme 20

Using this 1-pot method led to a more rapid synthesis of alkylidine malonates and a range of 20 compounds were synthesised in good to excellent yields. This allowed a moderate sized library of compounds to be effectively synthesised for acrylate ester synthesis. Limitations of the method appear to be some heterocycles such as furan and pyrrole which are sensitive to acid and light, respectively. Other problematic aldehydes are straight chain aliphatics which tend to self condense with a second equivalent of Meldrum's acid to give an insoluble solid. The 5-alkylidine malonates tended to be air and moisture stable, although a number of compounds degraded over a period of 6 months (*Table 1*).



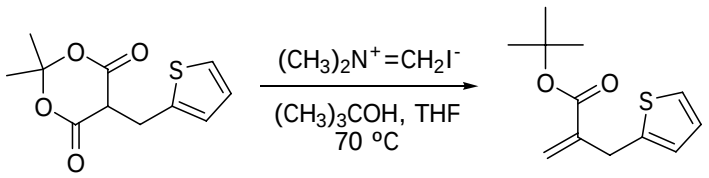
Entry	R^1	Yield [b]	Entry	R^1	Yield [b]
2.66[a]		88%	**2.79**		82%
2.71		87%	**2.80**		63%
2.72		88%	**2.81**		61%
2.73		91%	**2.82**		98%
2.74		87%	**2.83**		89%
2.75		94%	**2.84**		95%
2.76		73%	**2.85**		92%
2.77		76%	**2.86**		97%
2.78		64%	**2.87**		92%

[a] Typical reaction conditions: Aldehyde (45 mmol), Meldrum's acid (1.1 eq), H_2O (50 mL) followed by sodium borohydride (4 eq.), acetic acid (10 mL), dichloromethane (50 mL)
[b] Isolated yields

Table 1

Using the 5-benzyl substituted alkylidines, Mannich[37] type reactions could be explored. The main advantage of using a cyclic malonate species is the ability to open the ring with appropriate nucleophiles such as alcohols to give the corresponding ester. Coupled with a

Mannich reaction the loss of acetone, carbon dioxide and dimethylamine leads to product formation in high yields. The major advantage is the reaction by-products are volatile giving clean conversion to product. A range of conditions were studied, using *N*,*N*-dimethylmethyleneiminium iodide (Eschenmoser's iodide salt) which is one of the best known reagents for terminal alkene synthesis.[38] The *tert*-butyl ester functionality was chosen for the substrates due to its steric bulk and previous good results using isopropyl and cyclohexyl based esters.[23, 39] Using neat *tert*-butanol as a solvent led to incomplete dissolution of the Eschenmoser's salt. This is in comparison to using anhydrous methanol which gives complete conversion to the thiophene acrylate methyl ester (**2.88**) in 96% yield. The quantity of Eschenmoser's iodide (E.I.) was also critical, with 1.1 eq. giving poor yields while using an excess of 2.6 eq. gave optimal yields and atom efficiency and increasing quantities to 3.5 eq. gave no improvements to yield (*Table 2*).



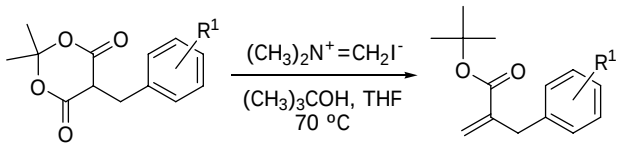
2.66 **2.88**

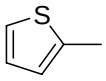
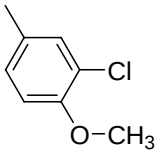
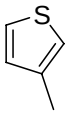
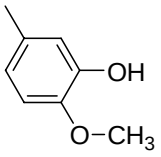
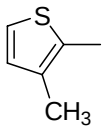
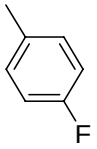
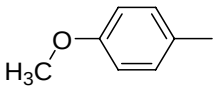
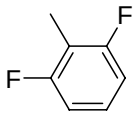
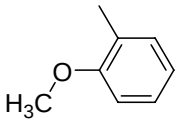
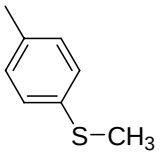
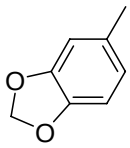
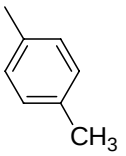
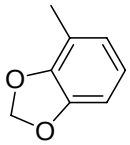
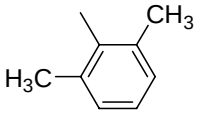
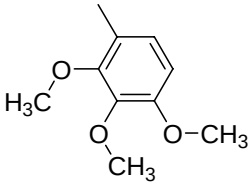
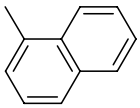
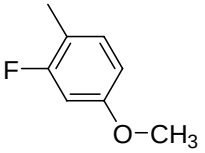
Entry	Eq. E.I.	Eq. t-BuOH	Temp	Yield [b]
1[a]	1.1	Neat	**65**	28
2	2.0	Neat	**65**	73
3	2.6	Neat	**70**	81
4	2.6	1:1 THF	**70**	89
5	2.6	1:1 THF	**Reflux**	68
6	3.5	1:1 THF	**70**	91

[a] Typical reaction conditions: Alkylidine malonate, Eschenmoser's iodide; solvent, temperature, 20 h
[b] Isolated yields

Table 2

A range of 5-benzyl alkylidines were then subjected to Mannich reaction. Upon dissolving the desired compound and Eschenmoser's iodide in a mixture of anhydrous THF and *tert*-butanol for optimum solubility with heating to 70 °C overnight, the desired product was obtained in greater than 95% purity after aqueous work-up. Although crude products can be used directly, purification *via* short flash column chromatography gave analytically pure materials. All acrylate esters were formed in good to high yields and products were stable to air and moisture with no isomerisation to the *tert*-butyl 2-methyl-3-phenylacrylate species (*Table 3*).



Entry	R^1	Yield [b]	Entry	R^1	Yield [b]
2.89[a]		92%	**2.98**		91%
2.90		82%	**2.99**		57%
2.91		78%	**2.100**		84%
2.92		95%	**2.101**		84%
2.93		94%	**2.102**		98%
2.94		90%	**2.103**		82%
2.95		87%	**2.104**		85%
2.96		88%	**2.105**		92%
2.97		83%	**2.106**		98%

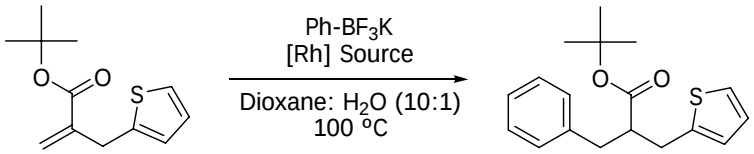
[a] Typical reaction conditions: Alkylidine malonate, Eschenmoser's iodide (2.6 eq), *tert*-butanol (10 mL), THF (10 mL), 70 °C, 20 h

[b] Isolated yields

Table 3

2.4 Racemic Conjugate-Addition – Trifluoroborates

From previous studies within the group it is known that potassium trifluoroborate salts are excellent coupling partners in rhodium-catalysed conjugate addition reactions giving high conversions to product and, in conjunction with a chiral ligand, good selectivity.[40, 41] Initial attempts at formation of thiophene-phenyl dibenzyl ester (**2.107**) using thiophenyl acrylate *tert*-butyl ester and potassium phenyltrifluoroborate with neutral rhodium catalyst [Rh(acac)(C_2H_4)$_2$] in dioxane-water gave a disappointing yield of 5%. It was felt that the significant blackening of the reaction was leading to an inactive rhodium-catalyst, so to improve stability a phosphine ligand was added. Upon adding either bisphosphine (dppb) or monophosphine (PPh_3) led to 86 and 61% yield, respectively, showing that addition of an aryl group with subsequent enolate protonation could be achieved. Genet and co-workers have previously shown that trifluoroborate conjugate-addition occurs most effectively with cationic rhodium sources such as [Rh(cod)$_2$][(PF_6)] and [Rh(cod)$_2$][(BF_4)].[42-44] In our hands using a range of cationic rhodium complexes with various counterions reaction occurred smoothly without additional achiral ligand. However, by adding a simple diene ligand such a cod led to a rapid accelerating effect, with complete conversion to product in 2 hours. Addition of phosphine ligand gave a similar yield but significantly reduced reaction time (*Table 4*).



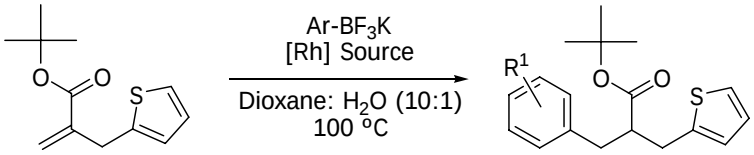
2.89 **2.107**

Entry	Rhodium Source	Ligand	Time h	Yield [b]
1[a]	[Rh(acac)(C_2H_4)$_2$]	-	18	<5%
2	[Rh(acac)(C_2H_4)$_2$]	dppb	6	86%
3	[Rh(acac)(C_2H_4)$_2$]	PPh_3	18	61%
4	[RhCl(cod)]$_2$	-	18	41%
5	[RhOH(cod)]$_2$	-	18	51%
6	[RhOH(cod)]$_2$	cod	18	67%
7	[Rh(cod)$_2$][(PF_6)]	-	18	62%
8	[Rh(cod)$_2$][(BF_4)]	-	18	59%
9	[Rh(cod)$_2$][(SbF_6)]	-	18	71%
10	[Rh(cod)$_2$][(SbF_6)]	cod	2	94%
11	[Rh(cod)$_2$][(SbF_6)]	dppb	6	81%

[a] Typical reaction conditions: tert-butyl acrylate, $PhBF_3K$ (2 eq), Rh source (3 mol %), Ligand (3.3 mol%). dioxane (1 mL) water (0.1 mL)
[b] Isolated yield

Table 4

With a functional reaction in hand, a small range of aryl potassium trifluoroborate salts were successfully coupled with thiophene acrylate *tert*-butyl ester. Using $[Rh(cod)_2][SbF_6]$ as a chiral ligand and an additive of 10% cod in dioxane-water, a number of electron rich and electron deficient boronates could be successfully coupled giving the α-α′-dibenzyl ester motif. It was found that sterically demanding boronate species such as 1- naphthyl and 2-naphthyl trifluoroborates could be coupled rapidly; electron rich and electron deficient species can be introduced albeit with slower reaction times. Highly electron deficient species such as the 3-nitrophenyl group required refluxing overnight in order to achieve significant quantities of product (*Table 5*).



Entry	Ar-BF_3K	Time h	Yield [b]
2.108[a]	1-Naphthyl	2	97%
2.109	2-Naphthyl	2	92%
2.110	4-CH_3CO-Ph	6	98%
2.111	3-NO_2-Ph	20	83%
2.112	4-Br-Ph	6	87%
2.113	3-Cl,4-OMe-Ph	6	89%

[a] Typical reaction conditions: tert-butyl acrylate, $ArBF_3K$ (2 eq), $[Rh(cod)_2][SbF_6]$ source (3 mol %), cod (10 mol%). dioxane (1 mL) water (0.1 mL)
[b] Isolated yield

Table 5

Determining enantioselectivity of the reaction with the optimised rhodium and proton sources was the next logical step of the assay. Chiral bidentate ligands were the initial choice for attempting an asymmetric variant as they have been widely utilised as effective chiral scaffolds for asymmetric catalysis.[2, 45, 46] A range of commercially available ligands were screened in the asymmetric 1,4-addition reaction of potassium phenyl trifluoroborate (*Figure* 6).

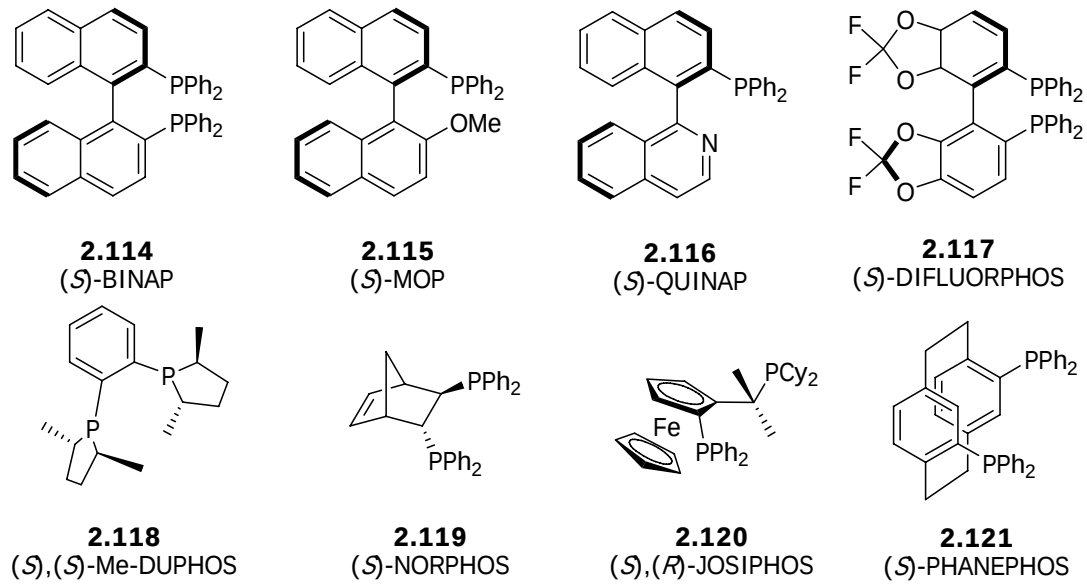
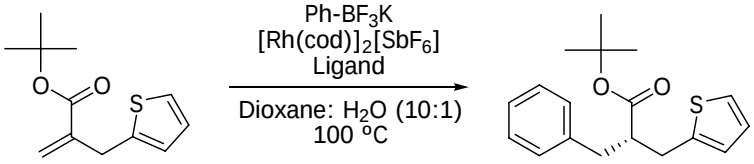


Figure 6

All reagents were added together in a 24 mL screw cap vial and stirred in dioxane and water at room temperature for 20 minutes. This allows the preforming of the cationic rhodium $[Rh(cod)(L^*)][SbF_6]$ which should act as the active species for asymmetric induction. After the catalyst formation the reaction mixture was transferred to a preheated heating block at 100 °C. This is necessary as previous results within the group show that enantioselectivity is lower when the sample is added cold and heated to the desired temperature.[47] Of the atropisomeric ligands used BINAP (**2.114**) gave the highest enantioselectivity at 38%. A number of similar binapthyl backbone ligands were used such as MOP (**2.115**), QUINAP (**2.116**) and DIFLUOROPHOS (**2.117**) giving a disappointing selectivity of 10-15%. Other ligands such as (Me)-DUPHOS (**2.118**), NORPHOS (**2.119**), JOSIPHOS (**2.120**) and PHANEPHOS (**2.121**) were also tried, giving poor selectivity of less than 5%. Reactions required extended reaction times of 20 h due to the decreased reactivity of the rhodium-phosphine ligand species (*Table 6*).

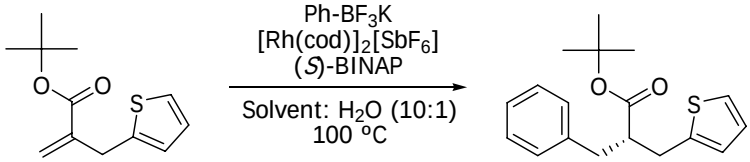


Entry	Ligand	Yield %	ee %	Entry	Ligand	Yield %	ee %
1[a]	(*S*)-BINAP	84[b]	38[c]	**5**	(*S*,*R*)-JOSIPHOS	81	<5
2	(*S*)-QUINAP	72	15	**6**	(*S*,*S*)-Me-DUPHOS	95	0
3	(*S*)-MOP	41	<5	**7**	(*S*)-NORPHOS	70	<5
4	(*S*)-DIFLUORPHOS	54	10	**8**	(S)-PHANPHOS	0	n/a

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2mmol), potassium trifluoro (phenyl)borate (2 eq), $[Rh(cod)_2][SbF_6]$ (3 mol%), chiral ligand (3.3 mol%) dioxane (1 ml), water (0.1 mL), 100°C, 20 hours.
[b] Isolated yields after flash chromatography
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH).

Table 6

Solvents were screened next in the catalytic process, due to the critical effect of solvent in rhodium-catalysed reactions with organotrifluoroborates.[23, 48] A number of non-coordinating solvents were used in the reaction to determine whether enantioselctivity could be improved. Using aprotic solvents such as benzene and toluene gave comparable yields and selectivity to dioxane. This result correlates well with previous work within the group on succinic ester derivatives where benzene gives highly enantioenriched products - 82% enantiomeric excess for the addition of 1-naphthyl organotrifluoroborate.[40] Of interest were the results for fluorobenzene and benzotrifluoride (BTF), which gave moderate selectivities for additions to dimethyl itaconate.[49] BTF in particular gave enantiomeric excess in comparison with dioxane although yields were moderate. Highly halogenated solvents such as dichloroethane and hydrocarbons gave no yield and selectivity. From the results it is clear that a number of solvents can be successfully used to achieve good yields and moderate selectivity. Using a polar solvent such as acetonitrile gives only low yields of racemic product (*Table* 7).



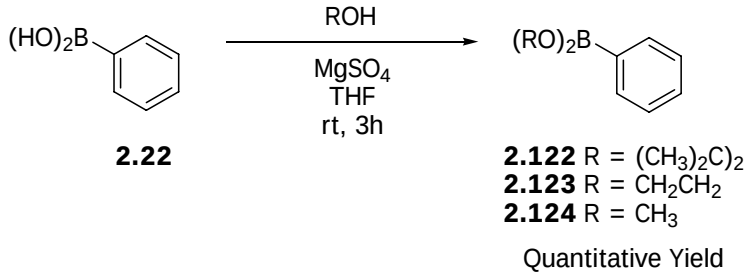
Entry	Solvent	Yield %	ee %
1	Dioxane	84[b]	38[c]
2	Benzene	71	32
3	Toluene	79	35
4	Fluorobenzene	63	19
5	BTF	59	37
6	Acetonitrile	20	0
7	Dichloroethane	Trace	n.d
8	Heptane	9[d]	n.d

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), potassium trifluoro(phenyl)borate (2 eq), $[Rh(cod)_2][PF_6]$ (3 mol%), (*S*)-BINAP (3.3 mol%) solvent (1ml), water (0.1 mL), 100°C, 18 hours.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH.
[d] Conversion by ^{1}H NMR

Table 7

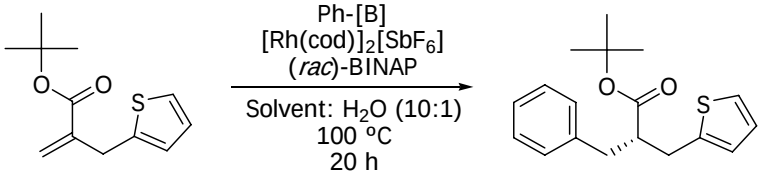
At this point it was felt that potassium trifluoroborate salts could be unreliable in a dioxane/water mixture as enantioselectivity was not reproducible. When setting up the reaction, incomplete dissolution of starting materials in the reaction vessel became a problem. Attempts to achieve a homogeneous solution with sonication proved unsuccessful. It was of interest to test whether other organoboron species might be more suitable for further methodology. Batey has shown that trifluoroborates with a tetrabutylammonium counterions act as highly soluble coupling reagents in organic solvents.[50] The commercially available phenyl trifluoroborate salt was dissolved in dichloromethane and addition of 1 equivalent of tetrabutylammonium hydroxide was added. The reaction mixture was stirred for 1 minute and extracted with dichloromethane to give pure tetrabutylammonium counterion boronate. A range of other coupling reagents were explored including commercially available phenyl boronic acid (**2.22**) and phenyl triethoxysiloxane. Such reagents have been previously used with success in conjugate addition reactions.[51, 52] Boronic esters were considered as alternative coupling reagents and pinacol boronic ester (**2.122**) was synthesised by stirring **2.22** in THF with pinacol and magnesium sulfate to remove water formed in reaction. The pinacol boronic ester could then be purified by silica gel chromatography to remove traces of

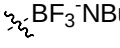
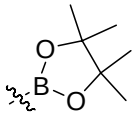
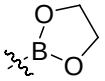
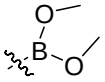
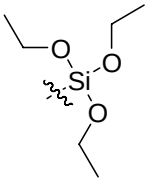
residual boronic acid. This method also worked effectively in the synthesis of the ethylene glycol variant (**2.123**) and methyl boronic ester (**2.124**) (*Scheme 21*).



Scheme 21

Combining a range of organometallics in the conjugate addition reaction to 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester with a $[Rh(cod)_2][SbF_6]$ catalyst and racemic BINAP as a chiral ligand showed that changing counterion of the organofluoroborate gave similar yields to the potassium variant. Using species based on sp^2 boron reagents showed a range of reactivity. Boronic acid species coupled to give the desired α-α′-dibenzyl ester in 91% yield. Forming a boronic ester species gave a range of product yields, with the best results achieved with boronic methyl ether species at 26% while the ethylene glycol system gave only a 12% yield and pinacol showed no reaction. This is due to the inability of boronic ester species to transmetallate effectively to the rhodium centre leading to reduced aryl transfer to the substrate. Finally, commercially available phenyl triethoxysiloxane was subjected to analogous conditions to the boronic acid species; such substrates tend to undergo rhodium-catalysed conjugate additions with cationic catalysts and so results showed a promising 63% yield, although this was not as effective as boronic acids. For further optimisation boronic acids were chosen as they were more soluble in organic solvents and greater numbers of substituted aryl groups were available commercially. In addition yields were generally similar to the equivalent potassium trifluoroborate species (*Table 8*).



Entry	Organometallic	Yield %
1[a]		78[b]
2		91
3		0
4		12
5		26
6		61

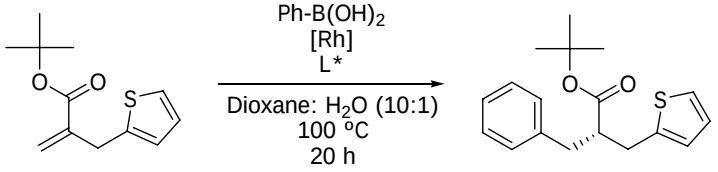
[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), organometallic (2 eq), $[Rh(cod)_2][SbF_6]$ (3 mol%), dioxane (1ml), water (0.1 mL), 100°C, 18 hours.
[b] Isolated yield

Table 8

2.5 Asymmetric Conjugate Addition – Boronic Acids

At this stage with a large amount of additional optimisation to be attempted a rapid route was required to give a good breadth of data. Microwave irradiation has proved to be a suitable method for accelerating catalytic reactions with metals.[53, 54] When using the standard reaction with 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester under microwave tubes capped under a stream of inert gas the rhodium-catalysed addition occurred in good yields with no loss in enantioselectivity in just 1 hour. A range of enantiopure ligands were screened with the two best rhodium catalysts $[Rh(cod)_2][SbF_6]$ and $[Rh(acac)(C_2H_4)_2]$, and optimum results were achieved with ligands containing a BINOL backbone, such as BINAP and DIFLUORPHOS, giving good enantioselectivity and yields (*Table 9*). Ligands with small chiral environments

such as (*R*)–PROPHOS and (*S*,*S*)–CHIRAPHOS gave low selectivity suggesting that a more sterically bulky chiral scaffold is required for higher enantioselectivity. Also of note is that (*S*,*S*)-Me-DUPHOS gives excellent yields in the conjugate-addition enolate protonation reaction with over 95% yield in one hour, unfortunately only racemic product was isolated.



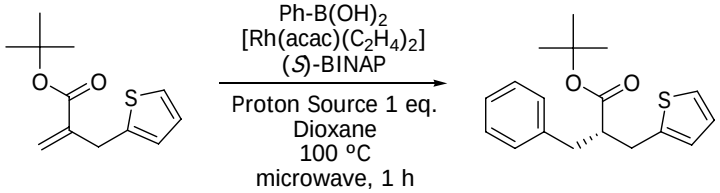
Entry	Rhodium Source	Ligand	Yield %	ee %
1[a]	$[Rh(cod)_2][SbF_6]$	(*S*)-BINAP	84%	34%
2	$[Rh(cod)_2][SbF_6]$	(*S*,*S*)-CHIRAPHOS	67%	21%
3	$[Rh(cod)_2][SbF_6]$	(*S*)-QUINAP	72%	15%
4	$[Rh(cod)_2][SbF_6]$	(*R*)-PROPHOS	51%	18%
5	$[Rh(cod)_2][SbF_6]$	(*S*)-DIFLUOROPHOS	54%	10%
6	$[Rh(cod)_2][SbF_6]$	(*S*,*S*)-Me-DUPHOS	98%	5%
7	***[Rh(acac)(C2H4)2]***	***(S)-BINAP***	***63%***	***58%***
8	$[Rh(acac)(C_2H_4)_2]$	(*S*,*S*)-CHIRAPHOS	42%	34%
9	$[Rh(acac)(C_2H_4)_2]$	(*R*)-PROPHOS	24%	29%
10	$[Rh(acac)(C_2H_4)_2]$	(*S*)-QUINAP	44%	18%
11	$[Rh(acac)(C_2H_4)_2]$	(*S*)-DIFLUOROPHOS	49%	56%
12	$[Rh(acac)(C_2H_4)_2]$	(*S*,*S*)-Me-DUPHOS	91%	<5%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (2 eq), [Rh] Source (3 mol%), Ligand (3.3 mol%) dioxane (1ml), water (0.1 mL), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 9

With a respectable chiral ligand and rhodium catalyst combination in hand, the choice of proton source was considered. Water had proved to be a reasonable choice with a 58% e.e. in conjunction with $[Rh(acac)(C_2H_4)_2]$ and (*S*)-BINAP. Upon reaction of 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester with *ortho*-substituted phenols, such as guiacol (2-methoxyphenol) and 2-hydroxy acetophenone in anhydrous dioxane a slight improvement in enantioselectivity was observed. Both of these systems are believed to give moderate chelation to the rhodium-centre through methoxy and acetyl group respectively.[23] The yields with *ortho*-substituted phenols proved to be lower than using water as a proton source; this was due to difficulties in separating phenol from product by column chromatography. Use of phthalimide, a nitrogen donating proton source used by Sibi *et al*[24] gave comparable enantioselectivity to water in this process. The final proton source examined was BINOL a commercially available chiral diol with both enantiomers readily available. Addition of (*S*)-BINOL (1 eq. to substrate) as a

proton source gave a moderate yield, but good selectivity (69% e.e.). The other enantiomer of BINOL was also employed to check for matched-mismatched combinations in the reaction. Employing (*R*)-BINOL as the proton source gave the same sense of enantioselectivity in the reaction, and using (*rac*)-BINOL gave identical results to its enantiopure derivatives. This suggests that the proton is not delivered from the proton source itself but by prior coordination to the rhodium species. The observation that using (*S*)-BINAP as the chiral ligand gives α-α′ dibenzyl esters with the same configuration is important in determining reactivity (*Table 10*).

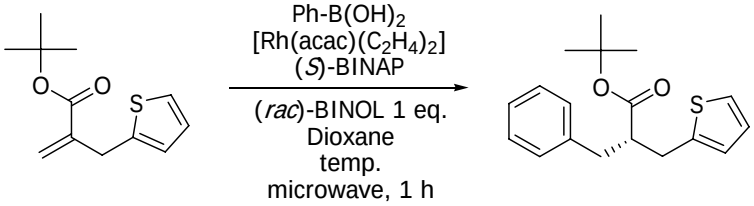


Entry	Proton Source	Yield %[b]	ee %[c]	Entry	Proton Source	Yield %[b]	ee %[c]
1[a]	Water	63%	58%	**5**	(*R*) -BINOL	47%	69%
2	Guiacol	54%	60%	**6**	(*S*) -BINOL	48%	69%
3	2-Acetophenone	42%	70%	**7**	(*rac*) -BINOL	45%	69%
4	Pthalimide	57%	62%				

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (4 eq), [Rh(acac)(C_2H_4)$_2$] Source (3 mol%), (*S*)-BINAP (3.3 mol%), proton source (1 eq), dioxane (1 ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 10

In order to examine whether enantioselectivity could be further improved the variable of temperature was investigated. Sibi and co-workers have shown that lowering temperatures to 50 ºC gives improved chiral induction.[24] Subjecting 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester to [Rh(acac)(C_2H_4)$_2$] and (*S*)-BINAP at extremes of temperature (50 ºC and 140 ºC) leads to no reactivity, with low temperatures giving incomplete dissolution and high temperatures giving degradation of rhodium catalyst. At 100 ºC there is a reproducible enantioselectivity of 68% e.e while at 120 ºC yield is slightly improved but enantioselectivity is reduced to 29% e.e. (*Table 11*).

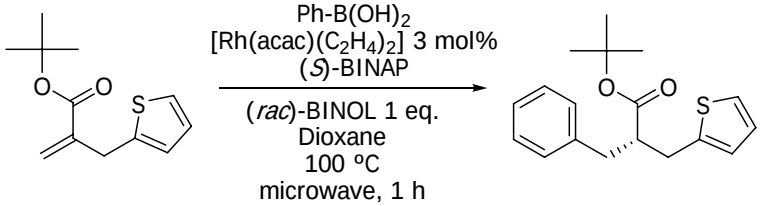


Entry	Temperature (°C)	Yield %[b]	ee %[c]
1[a]	50	n/r	n/a
2	80	34%	29%
3	100	45%	68%
4	120	49%	28%
5	140	n/r	n/a

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (4 eq), [Rh(acac)(C_2H_4)$_2$] Source (3 mol%), (*S*)-BINAP (3.3 mol%), (*rac*)-BINOL (1 eq), dioxane (1ml), temp °C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 11

Genet and co-workers have shown that the quantity of chiral ligand can have an effect on enantioselectivity.[55] Changing the amount of (*S*)-BINAP from 1.1 eq. to 2.2 eq. compared to rhodium catalyst gives an increase in selectivity by 6% to greater than 90% e.e. Comparison of a range of rhodium/ligand permeations shows that using no ligand leads to a low yield of product. Using more than 2.2 eq. of ligand does not lead to improved enantioselectivity, in fact yield and selectivity are substantially lowered, and using 5 eq. of chiral ligand gives similar results. This result suggests that increasing the quantity of ligand may give a bulky chiral environment. For α-α′ dibenzyl esters the substrate is congested with the close proximity of the *tert*-butyl ester group and aromatic ring. Using 1.5 eq of ligand to rhodium gives optimum results in this system – 61% yield, 71% e.e (*Table 12*).

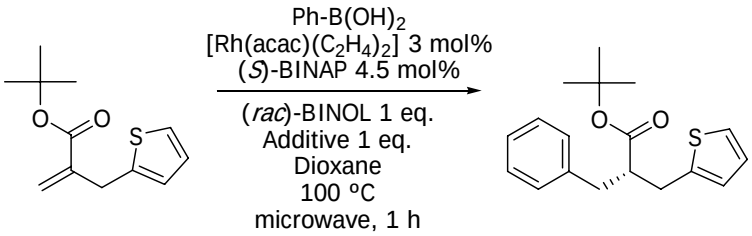


Entry	mol% BINAP	Yield %	ee %
1[a]	No ligand	8%	0%
2	(*S*)-BINAP 1.1 eq.	48%	69%
3	(*S*)-BINAP 1.5 eq.	50%	71%
4	(*S*)-BINAP 2.2 eq.	49%	63%
5	(*S*)-BINAP 5 eq.	40%	62%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.2 mmol), phenyl boronic acid (4 eq), [Rh(acac)(C_2H_4)$_2$] Source (3 mol%), (*S*)-BINAP, (*rac*)-BINOL (1 eq), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 12

The next variable under investigation was the addition of an additive to the reaction. In previously published rhodium-catalysed conjugate addition reactions, addition of base leads to improvements in yield and selectivity.[56] Combining 3 mol% [Rh(acac)(C_2H_4)$_2$] and 4.5 mol% (*S*)-BINAP with 1 eq. of (*rac*)-BINOL and 1 eq. of additive under microwave irradiation for 1h gives a range of results (*Table 13*). Addition of an acidic additive such as tosylic acid (TsOH) leads to no product formation due to probable poisoning of catalyst. Inorganic bases generally gave a 10% improvement in reaction yields and selectivity with no improvement in reactivity. Addition of an oxazolidinone such as chiral auxillary SuperQuat,[57, 58] also gives slight improvement in e.e. to 70%. Of most interest is the addition of 1 equivalent of boric acid to the reaction, which can act as an additional proton source. Yields and reactivity with boric acid led to a marginal improvement in yield and selectivity, and therefore boric acid was studied more extensively as a viable proton source.

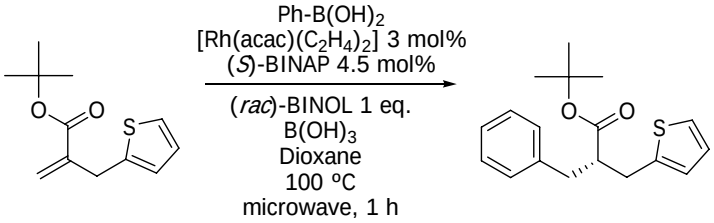


Entry	Proton Source	Additive	Yield %	*ee* %
1[a]	(*rac*)-BINOL	n/a	50%	70%
2	(*rac*)-BINOL	TsOH	n/r	n/a
3	(*rac*)-BINOL	$B(OH)_3$	62%	72%
4	(*rac*)-BINOL	K_3CO_3	58%	70%
5	(*rac*)-BINOL	K_3PO_4	57%	68%
6	(*rac*)-BINOL	NaF	60%	70%
7	(*rac*)-BINOL	SuperQuat	48%	70%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (4 eq), [Rh(acac)(C_2H_4)$_2$] Source (3 mol%), (*S*)-BINAP (4.5 mol%), (*rac*)-BINOL (1 eq), additive (1 eq.), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 13

At this stage boric acid equivalents were studied in the reaction of 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester with [Rh(acac)(C_2H_4)$_2$] and (*S*)-BINAP. Mixing (*rac*)-BINOL with either 1.1 or 5 eq. of boric acid leads to an improvement in both yield and selectivity. This could be due in part to the increased quantity of proton source in the reaction, as it was observed that the chiral environment of BINOL has no influence on reaction selectivity. To this end, removal of (*rac*)-BINOL and replacement with 1, 2, 3, 5 and 10 equivalents of boric acid to substrate gives an increase in yield to a plateau of 85% and an improvement of e.e. to 80% (*Table 14*). From these results it was found that boric acid was the proton source of choice for tandem rhodium-catalysed addition enolate protonation reactions to *tert*-butyl substituted benzyl acrylates. A further advantage of replacing BINOL with boric acid as the latter may be obtained as an inexpensive bulk chemical.



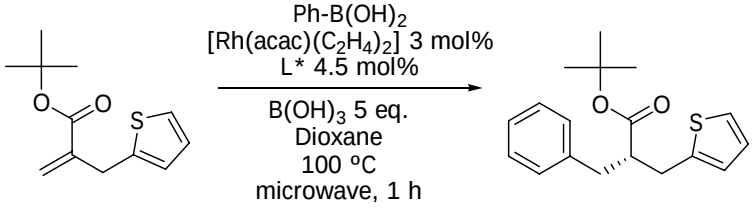
Entry	Proton Source	Additive	Yield % [b]	*ee* % [c]
1[a]	(*rac*)-BINOL	n/a	56%	71%
2	(*rac*)-BINOL	$B(OH)_3$ 1.1 eq.	60%	71%
3	(*rac*)-BINOL	$B(OH)_3$ 5.0 eq.	73%	76%
4	-	$B(OH)_3$ 1.1 eq.	40%	71%
5	-	$B(OH)_3$ 2.0 eq.	43%	78%
6	-	$B(OH)_3$ 3.0 eq.	65%	79%
7	-	$B(OH)_3$ 5.0 eq.	84%	80%
8	-	$B(OH)_3$ 10.0 eq.	85%	80%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (4 eq.), $[Rh(acac)(C_2H_4)_2]$ Source (3 mol%), (*S*)-BINAP (4.5 mol%), (*rac*)-BINOL (1 eq), $B(OH)_3$, dioxane (1 ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 14

Final conditions were now optimised with the best ligand ratio and proton source variants determined. A range of different rhodium sources were used incorporating more labile diene ligands such as nbd, or ethylene groups, which should be more likely to be displaced by the chiral phosphine ligand (*Table 15*). Using $[Rh(nbd)Cl]_2$ dimer as a catalyst gives 56% yield and 69% e.e. suggesting that active catalyst species is not reformed as rapidly as $[Rh(acac)(C_2H_4)]$, similar results are observed for cationic catalyst $[Rh(nbd)_2][BF_4]$. Using highly active catalysts such as $[Rh(C_2H_4)_2Cl]_2$ where ethylene is rapidly lost on complex formation an improvement in yield to 88% is observed in the reaction of 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester and phenyl boronic acid, enantioselectivity is generally similar to complexes with acac ligands. A range of atropisomeric ligands were also screened with $[Rh(acac)(C_2H_4)_2]$, using ligands where the phosphines contain bulky aryl substituents such as (*S*)-*tol* BINAP and (*S*)-*xylyl* BINAP, it was observed that selectivity and yields are reduced as steric bulk increases. This is due to the congestion of the phosphine groups around the ligand leading to incomplete complexation to the rhodium complex. A brief study of electronic effects on the phosphine backbone was explored with electron-rich phosphine ligands such as (*S*)-SYNPHOS giving excellent yields and selectivity. (*S*)-DIFLUORPHOS, pioneered by Genet *et al*,[59] was also included as this ligand-rhodium combination is known to

give excellent selectivity in the synthesis of β^2-amino acids.[24] In our hands DIFLUORPHOS gives yields in the same region as (*S*)-BINAP, but selectivity is slightly reduced (76%). Finally, comparison with a chiral diene ligand based on optically pure carvone (*R,R,R*)-DOLEFIN, established by Carreira,[60] gives a disappointing enantiomeric excess of 52%. It is unknown whether this is due to a difference in chiral environment around the rhodium centre or due to incomplete complexation due to the inability of the ligand to displace acac from the initial rhodium-complex.

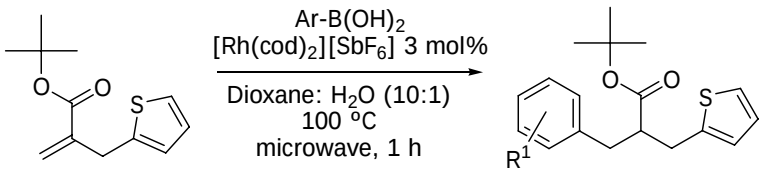


Entry	Rhodium Source	Ligand	Yield % [b]	*ee* % [c]
1[a]	$[Rh(acac)(C_2H_4)_2]$	(*S*)-BINAP	84%	80%
2	$[Rh(acac)(C_2H_4)_2]$	(*R*)-BINAP	81%	-79%
3	$[Rh(nbd)Cl]_2$	(*S*)-BINAP	56%	69%
4	$[Rh(C_2H_4)_2Cl]_2$	(*S*)-BINAP	88%	78%
5	$[Rh(nbd)_2][BF_4]$	(*S*)-BINAP	47%	53%
6	$[Rh(acac)(C_2H_4)_2]$	(*S*)-*tol* BINAP	54%	68%
7	$[Rh(acac)(C_2H_4)_2]$	(*S*)-*xylyl* BINAP	69%	62%
8	$[Rh(acac)(C_2H_4)_2]$	(*S*)-SYNPHOS	71%	72 %
9	$[Rh(acac)(C_2H_4)_2]$	(*S*)-DIFLUORPHOS	80%	76%
10	$[Rh(acac)(C_2H_4)_2]$	(*R,R,R*) DOLEFIN	76%	-52%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), phenyl boronic acid (4 eq), [Rh] Source (3 mol%), Ligand (4.5 mol%), $B(OH)_3$ (5 eq.), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 15

With conditions optimised a range of α,α′-dibenzyl esters with a variety of substituted aryl groups could be synthesised from 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester and the corresponding aryl boronic acid. For racemic samples a catalyst system of $[Rh(cod)_2][SbF_6]$ in a mixture of dioxane/water (10:1) was an excellent catalyst system with high yields observed for a range of compounds. This system was equally effective in both thermal and microwave assisted heating methods. A large number of electron rich and electron deficient substituents were tolerated on the aryl ring and sensitive functionality such as aldehydes, halogens, nitrile and thioether were readily tolerated with no degradation product observed (*Table 16*).



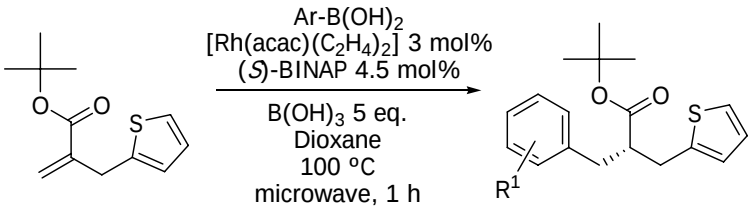
Entry	Boronic Acid	Rhodium Source	Yield % [b]	*e.e.* %
2.107[a]	Ph-	$[Rh(cod)_2][SbF_6]$	91%	*rac*
2.108	1-Naphthyl	$[Rh(cod)_2][SbF_6]$	97%	*rac*
2.109	2-Naphthyl	$[Rh(cod)_2][SbF_6]$	92%	*rac*
2.110	4-Acetyl Ph	$[Rh(cod)_2][SbF_6]$	98%	*rac*
2.111	3-NO_2 Ph	$[Rh(cod)_2][SbF_6]$	83%	*rac*
2.112	4-Br Ph	$[Rh(cod)_2][SbF_6]$	87%	*rac*
2.113	3-Cl 4-OMe Ph	$[Rh(cod)_2][SbF_6]$	89%	*rac*
2.125	Biphenyl	$[Rh(cod)_2][SbF_6]$	76%	*rac*
2.126	4-*t*-Bu Ph	$[Rh(cod)_2][SbF_6]$	94%	*rac*
2.127	4- Formyl Ph	$[Rh(cod)_2][SbF_6]$	79%	*rac*
2.128	3,5 (CF_3) Ph	$[Rh(cod)_2][SbF_6]$	85%	*rac*
2.129	3-CF_3 Ph	$[Rh(cod)_2][SbF_6]$	93%	*rac*
2.130	3,5 Difluoro Ph	$[Rh(cod)_2][SbF_6]$	92%	*rac*
2.131	4-OCF_3 Ph	$[Rh(cod)_2][SbF_6]$	94%	*rac*
2.132	3,5 Dichloro Ph	$[Rh(cod)_2][SbF_6]$	92%	*rac*
2.133	4-OMe Ph	$[Rh(cod)_2][SbF_6]$	82%	*rac*
2.134	3-Methylendioxy	$[Rh(cod)_2][SbF_6]$	86%	*rac*
2.135	4-SMe Ph	$[Rh(cod)_2][SbF_6]$	83%	*rac*
2.136	4-CN Ph	$[Rh(cod)_2][SbF_6]$	91%	*rac*

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), aryl boronic acid (4 eq), $[Rh(cod)_2][SbF_6]$ (2 mol%), dioxane (1ml), water (0.1 mL), 100°C, microwave 110W, 1 hour.
[b] Isolated yields

Table 16

Upon subjecting a similar range of boronic acids to the enantioselective conditions it was pleasing to note that good reactivity was still observed. Yields were generally lower in the chiral examples due to the lower turnover of the rhodium-phosphine complexes, compared to rhodium-diene species. A large number of electron rich and electron deficient species were incorporated into the final structures with enantioselectivity consistently 80-85% (*Table 17*). Highest yield and selectivity was obtained with 4-*tert*-butyl phenyl boronic acid affording the corresponding α,α′-dibenzyl ester in 93% yield and 86% e.e. There are 2 notable exceptions in the chiral methodology; using 1-naphthene boronic acid under optimised conditions gives a near racemic product in 15% yield. This is due to the steric demands of the 1-naphthalene moiety in this example, comparing to the 2-naphthalene derivative (80% yield 84% e.e.) where steric demands are reduced gives excellent results. The second example involves 3-nitrophenyl boronic acid which gives no conversion to product. It is not clear why this is the case on

electronic grounds as other electron deficient species are tolerated in the process. One possible explanation could lie in the number of equivalents of boronic acid used, with a large excess it is possible that the rhodium species could become bound to the nitro group leading to no active catalyst turnover.



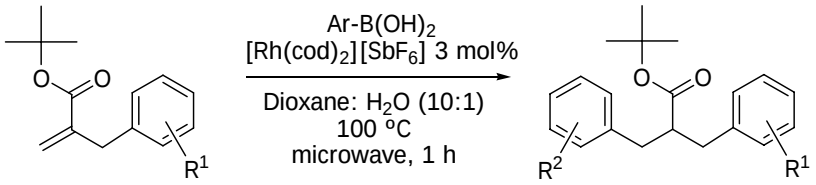
Entry	Boronic Acid	Yield % [b]	*e.e.* % [c]
2.107[a]	Ph-	74%	80%
2.108	1-Naphthyl	15%	<5%
2.109	2-Naphthyl	80%	84%
2.110	4-Acetyl Ph	68%	83%
2.111	3-NO_2 Ph	n/r	n/a
2.112	4-Br Ph	73%	84%
2.113	3-Cl 4-OMe Ph	81%	77%
2.125	Biphenyl	69%	82%
2.126	4-*t*-Bu Ph	93%	86%
2.127	4- Formyl Ph	71%	86%
2.128	3,5 $(CF_3)_2$ Ph	78%	85%
2.130	3,5 Dichloro Ph	50%	78%
2.133	4-OMe Ph	93%	82%
2.134	3-Methylendioxy	68%	78%
2.135	4-SMe Ph	81%	81%
2.136	4-CN Ph	72%	79%

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), aryl boronic acid (4 eq), [Rh] Source (3 mol%), Ligand (4.5 mol%), $B(OH)_3$ (5 eq.), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 17

With a good range of enantioselectivity observed using 2-thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester as the substrate and varying the boronic acid component of the reaction, it was important to extend the scope to other acrylate substrates with a single boronic acid used. The choice to test this reaction was 2-naphthlene boronic acid due to its consistent yields and selectivity with the 2-thiophenyl acrylate substrate. A number of previously synthesised acrylate esters were screened in the process, each encompassing a range of electron rich and electron deficient functionalities as well as steric effects on the aryl ring. Substrates with functional groups in the 2-position of the substrate were deemed an important consideration as

general difficulty in coupling 2-substituted boronic acids is generally observed due to steric effects. Subjecting a number of acrylate esters to standard racemic conditions of $[Rh(cod)_2][SbF_6]$ (3 mol%) and 2-naphthyl boronic acid (2 eq.) in dioxane/water (10:1) at 100°C for 1 hour under microwave conditions gave excellent yields for substrates based on 3-thiophenyl and 2-thiophenyl-3-methyl acrylate esters. A number of other structures based on phenyl rings with a range of different substitution patterns also gave yields in the region of 85-90% (*Table 18*).



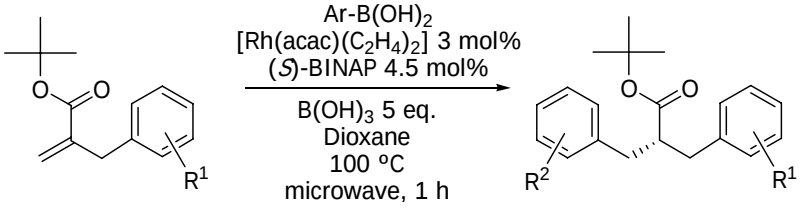
Entry	Substrate	Boronic Acid	Yield % [b]	*e.e.* %
2.137 [a]	3-Thiophenyl	2-Naphthyl	72	*rac*
2.138	2-Thiophenyl, 3-Me	2-Naphthyl	82	*rac*
2.139	2-OMe Ph	2-Naphthyl	87	*rac*
2.140	4-OMe Ph	2-Naphthyl	91	*rac*
2.141	4-OMe Ph	4-SMe Ph	84	*rac*
2.142	2,3,4-OMe Ph	2-Naphthyl	91	*rac*
2.143	4-SMe Ph	2-Naphthyl	80	*rac*
2.144	1-Naphthyl Ph	2-Naphthyl	91	*rac*
2.145	4-F Ph	2-Naphthyl	88	*rac*
2.146	2,6 F-Ph	2-Naphthyl	86	*rac*

[a] Reaction Conditions : 2-thiophen-2-ylmethyl-acrylic acid tert-butyl ester (0.2 mmol), aryl boronic acid (4 eq), [Rh] Source (3 mol%), Ligand (4.5 mol%), $B(OH)_3$ (5 eq.), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields

Table 18

After obtaining promising results with racemic conditions, attention was turned to the asymmetric protonation variant. A number of acrylate esters were subjected to the asymmetric conditions of $[Rh(acac)(C_2H_4)_2]$, enantiopure (*S*)-BINAP and boric acid as a proton source good to excellent enantioselectivity was achieved (*Table 19*). Lower enantioselectivity was observed for the 3-thiophenyl variant compared to previously used 2-substituted analogue. This may be due to a nearby coordinating effect of sulfur to rhodium in the 2-thiophenyl species giving better stability to the rhodium oxa-π-allyl species which is lost in other variants but is not confirmed. Similar results were observed when a methyl group is introduced into the 3-position of the heteroaryl ring. It is possible that the methyl group disrupts the coordination

by steric effects leading to decreased selectivity (63% e.e.). It appears that the most effective substrates for conjugate addition of 2-naphthyl boronic acid are electron rich materials such as 2- and 4-methoxybenzyl acrylates each giving just over 80% e.e. These materials also show that position of the groups around the aryl ring make little difference in the enantioselectivity obtained which could allow a number of more highly substituted acrylates to be used in reactions where the corresponding boronic acid analogues fail. Changing the electronic properties of the acrylate by adding fluorine groups causes a decrease in enantioselectivity from 4-fluoro to 2,6-difluorobenzyl acrylate. This observation could be due to the removal of electron density from the acrylate ester leading to weak coordination of the rhodium-species. The most impressive use of this methology is the addition of 2-naphthyl boronic acid to 1-naphthyl acrylate ester. The reaction proceeds smoothly under standard asymmetric conditions to give the final product in 86% yield and 78% e.e. This was seen as one of the most successful results of the asymmetric protonation methodology, due to the high steric demands of the substrate and lack of coordinating groups, such a high e.e. shows tandem processes are a powerful technique for synthesising compounds that would be difficult to produce by other means such as asymmetric hydrogenation.[61]



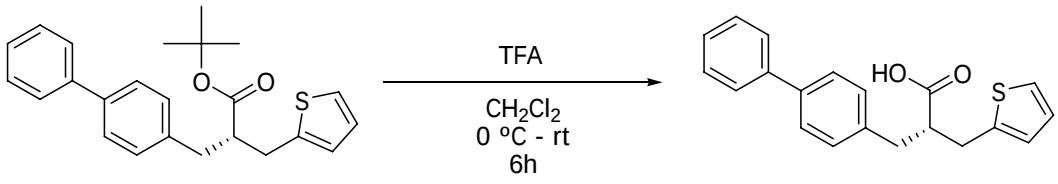
Entry	Substrate	Boronic Acid	Yield %	*e.e.* %
2.137 [a]	3-Thiophenyl	2-Naphthyl	61	59
2.138	2-Thiophenyl, 3-Me	2-Naphthyl	64	63
2.139	2-OMe Ph	2-Naphthyl	71	82
2.140	4-OMe Ph	2-Naphthyl	74	84
2.141	4-OMe Ph	4-SMe Ph	70	74
(*ent*)- 2.141	4-SMe Ph	4-OMe Ph	67	58
2.143	4-SMe Ph	2-Naphthyl	80	Inseparable
2.144	1-Naphthyl	2-Naphthyl	86	78
2.145	4-F Ph	2-Naphthyl	83	77
2.146	2,6 F-Ph	2-Naphthyl	69	62

[a] Reaction Conditions : 2-benzyl-acrylic acid tert-butyl ester (0.2 mmol), aryl boronic acid (4 eq), [Rh] Source (3 mol%), Ligand (4.5 mol%), $B(OH)_3$ (5 eq.), dioxane (1ml), 100°C, microwave 110W, 1 hour.
[b] Isolated yields
[c] Determined by HPLC analysis using chiral column (Chiralpak OD-H) 99:1 Hexane:2-PrOH

Table 19

2.6 Crystallography and Mechanistic Rationale

A range of α,α′-dibenzyl esters have been successfully synthesised *via* a tandem rhodium-catalysed enolate protonation methodology, however, at this point the "sense" of the chiral centre was yet to be determined. Unfortunately no similar structures to the newly formed dibenzyl esters had been previously undertaken. Negatively signed optical rotation values suggested that the absolute configuration of all compounds synthesised was the same, but a quantitative analysis was required. The only method to elucidate the chiral centre at the α-position was to determine the absolute stereochemistry by X-ray crystallography. Almost all of the structures elucidated were oils, due to the lipophilic nature of the *tert*-butyl group. Subjecting chiral 3-biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (**2.125**) to a solution of trifluoroacetic acid in dichloromethane for 6 hours gave quantitative conversion to the corresponding carboxylic acid (**2.147**) as a white semi-solid (*Scheme 22*).



2.125
69% yield
82% e.e.

2.147
94% yield
96% e.e. (1 Recrystallisation)

Scheme 22

A single recrystallisation from hot ethanol with controlled evaporation of solvent yielded crystals suitable for X-ray analysis. The TFA salt of 3-biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid was shown to have the structure below (*Figure 7*). The crystal structure confirms the absolute configuration of the compound to be (*S*)-. This was in good agreement with other examples of enolate protonation with succinic esters and amino acid derivatives.[23, 24, 62] Of interest from the crystal structure is that the 2 benzyl motifs in the molecule are aligned so as to maximise space around the α-position of the acrylate suggesting a large coordination region for the rhodium-species prior to coordination. The sulfur on the thiophene motif sits directly above the proton introduced by enantioselective protonation suggesting a possible coordination influence of the sulfur to the rhodium centre.

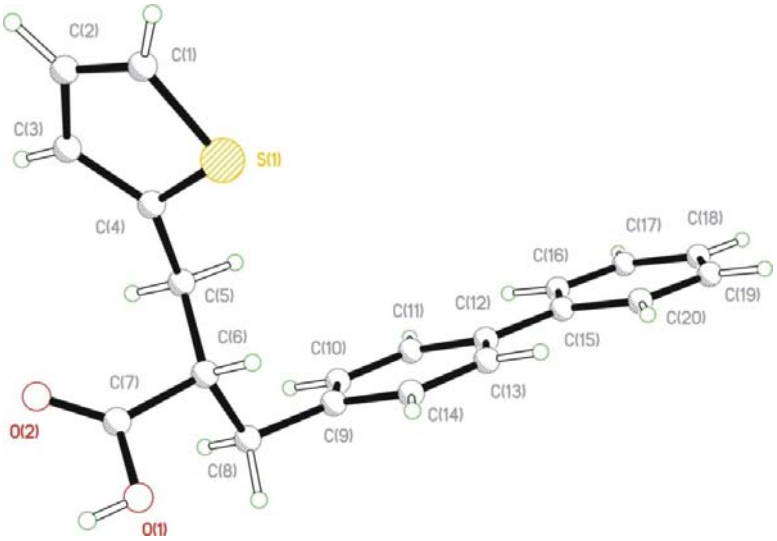
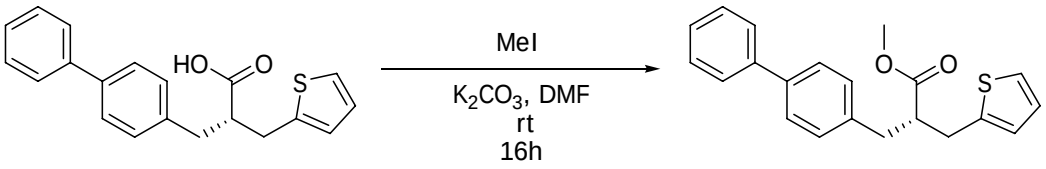


Figure 7

The recrystallisation of the carboxylic acid species should also lead to enantioenrichment of (*S*)-3-biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid (**2.147**). The corresponding carboxylic acid species was not soluble in solvents suitable for HPLC analysis, thus the methyl ester was synthesised using iodomethane, with potassium carbonate as a base in anhydrous DMF. This gave the desired methyl ester (**2.148**) in 96% yield after column chromatography. Comparison of the chiral species to the racemic material synthesised by rhodium-catalysed addition of 4-biphenyl boronic acid to 3-biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid methyl ester showed that enantiomeric excess could be improved to 96% e.e. This will allow the enantioenrichment of other such carboxylic acids to levels suitable for chiral building block materials (*Scheme 23*).



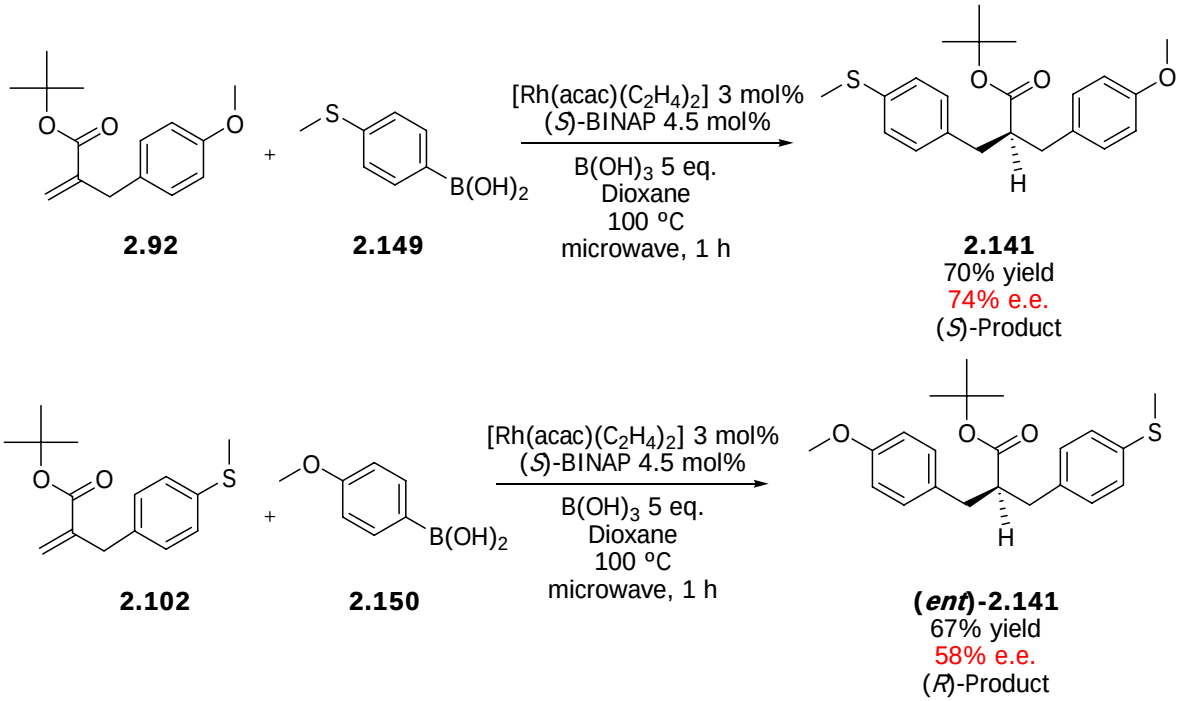
2.147

2.148
96% yield
96% e.e. by HPLC

Scheme 23

A final experiment was to ascertain whether the choice of acrylate ester or boronic acid was critical in the selectivity observed in the α,α′-dibenzyl products. Reacting 2-(4-methoxy-benzyl)-acrylic acid *tert*-butyl ester (**2.92**) with 4-methylsulfanylphenyl boronic acid (**2.149**)

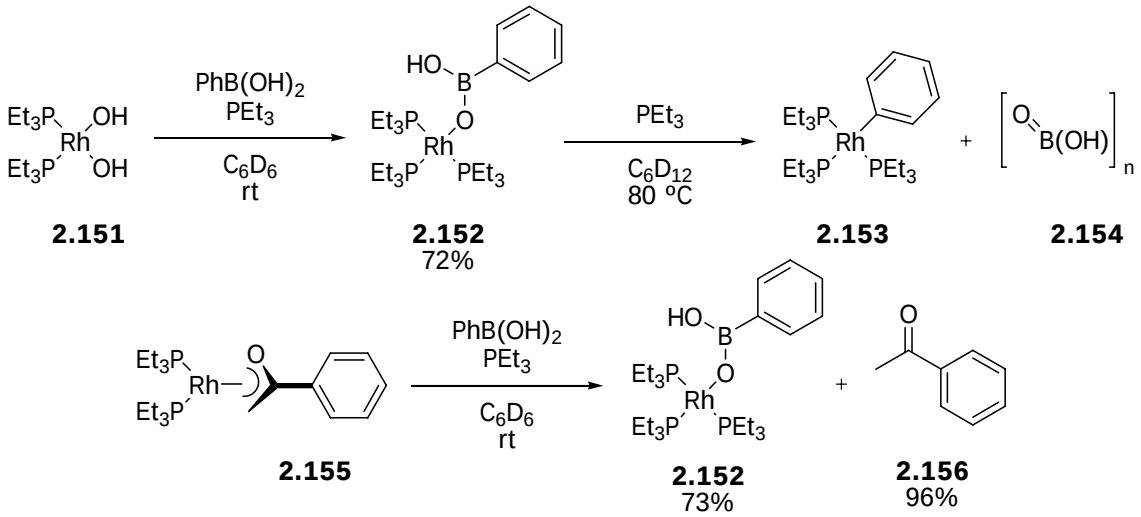
and the respective 2-(4-methylsulfanyl-benzyl)-acrylic acid *tert*-butyl ester (**2.102**) and 4-methoxyphenyl boronic acid (**2.150**), a cross-over experiment to determine enantioselectivity was attempted. The two acrylate esters and their corresponding boronic acid coupling partners were treated under standard asymmetric conditions, using 4-methylsulfanylphenyl boronic acid as a coupling partner gave improved e.e. values compared to the analogous acrylate ester. In each case the use of the methylsulfanyl group did not lead to poisoning of the rhodium catalyst with good yields observed for both reactions. By studying the HPLC data both products **2.141** and **(*ent*)-2.141** were obtained in moderate selectivity (*Scheme 24*).



Scheme 24

The least understood area of the reaction is the protonation of the oxa-π-allyl rhodium species formed upon insertion of the aryl fragment into the acrylate substrate. In simple substrates such as cyclohexenone, which has been extensively studied in conjugate-addition reaction methodology, water protonates the substrate in a racemic manner and is of less importance.[3, 63] The addition of boric acid to the reaction mixture leads to an improvement in both yield and enantioselectivity when compared to using BINOL as a proton source. It is unknown whether boric acid can complex to rhodium, giving a suitable proton for enolate quenching or acts as a proton source from bulk solution in enolate protonation chemistry. Previous results from Hartwig *et al* show a plausible mechanism for the transmetallation of organometallics to

a rhodium centre.[64] These studies put forward a new mechanistic insight into the catalytic process. The reaction is thought to occur by reaction of the product enolate with water to form a rhodium hydroxide complex, followed by transmetallation between the rhodium hydroxide and the boronic acid. Using $[(PEt_3)_2Rh(\mu\text{-}OH)]_2$ (**2.151**) as the rhodium precursor in the reaction followed by addition of phenyl boronic acid (**2.22**) gave a stable rhodium boronic acid species (**2.152**). These compounds could be isolated and crystal structures obtained. The rhodium complexes to the boronic acid initially *via* the oxygen atom, subsequent heating leads to the corresponding aryl-rhodium species (**2.153**) with insoluble boroxin oligomers (**2.154**) formed as the side-product. Additionally, reaction under the same conditions with rhodium enolate species (**2.155**) leads to a similar boron complex with the loss of acetophenone (**2.156**) implying that the transmetallation can occur directly with the enolate complex without the intermediary hydroxo complex (*Scheme 25*).



Scheme 25

By applying similar ideas to our rhodium catalysed methodology in conjunction with our findings a tentative mechanism can be proposed (*Figure 8*). The catalytic cycle begins with formation of the hydroxyl-enantiopure ligand rhodium species (**2.157**) as observed by Hayashi in his initial mechanism communication.[3] After transmetallation of the boronic acid (**2.158**) and subsequent complexation of the benzyl acrylate ester (**2.159**) an oxa-π-allyl species (**2.160**) is formed. This species is likely to be in equilibrium with the η^1-carbon bound rhodium complex (**2.161**) which is the key intermediate in the synthesis. This rhodium-alkyl species is unstable but has a free coordination site in this state which can be filled with a

further boronic acid or boric acid species (**2.162**). In the case of boric acid the species can eliminate as observed by Hartwig *et al* to give a rhodium hydride species (**2.163**) with loss of insoluble boroxin polymer solids (**2.154**). This active complex can subsequently deliver the "proton" to the α-position with facial selectivity defined by the chiral diphosphine. This step is highly dependent on the the η^1-carbon bound rhodium complex with high enantioselectivity only being obtained when a stable complex is formed. In the case of *tert*-butyl acrylate ester species, this appears to be the case when electron rich benzyl acrylates are used, such as thiophenyl and *para*-methoxy benzyl (~80% e.e.), whereas electron deficient species such as 2,6-difluorobenzyl acrylates give lower enantioselectivity. This could be due to electron density donated through the σ-donating ligand giving a more stable species. Upon delivering the proton to the α-position of the substrate defining the chiral centre (**2.164**), the rhodium species is regenerated by the action of boronic acid, boric acid or water leading to the regeneration of the active catalyst species (**2.157**). It is felt that using other systems such as phenols and water lead to protonation of the rhodium species before the asymmetric hydride transfer can be achieved due to excess water or acidic media being used.

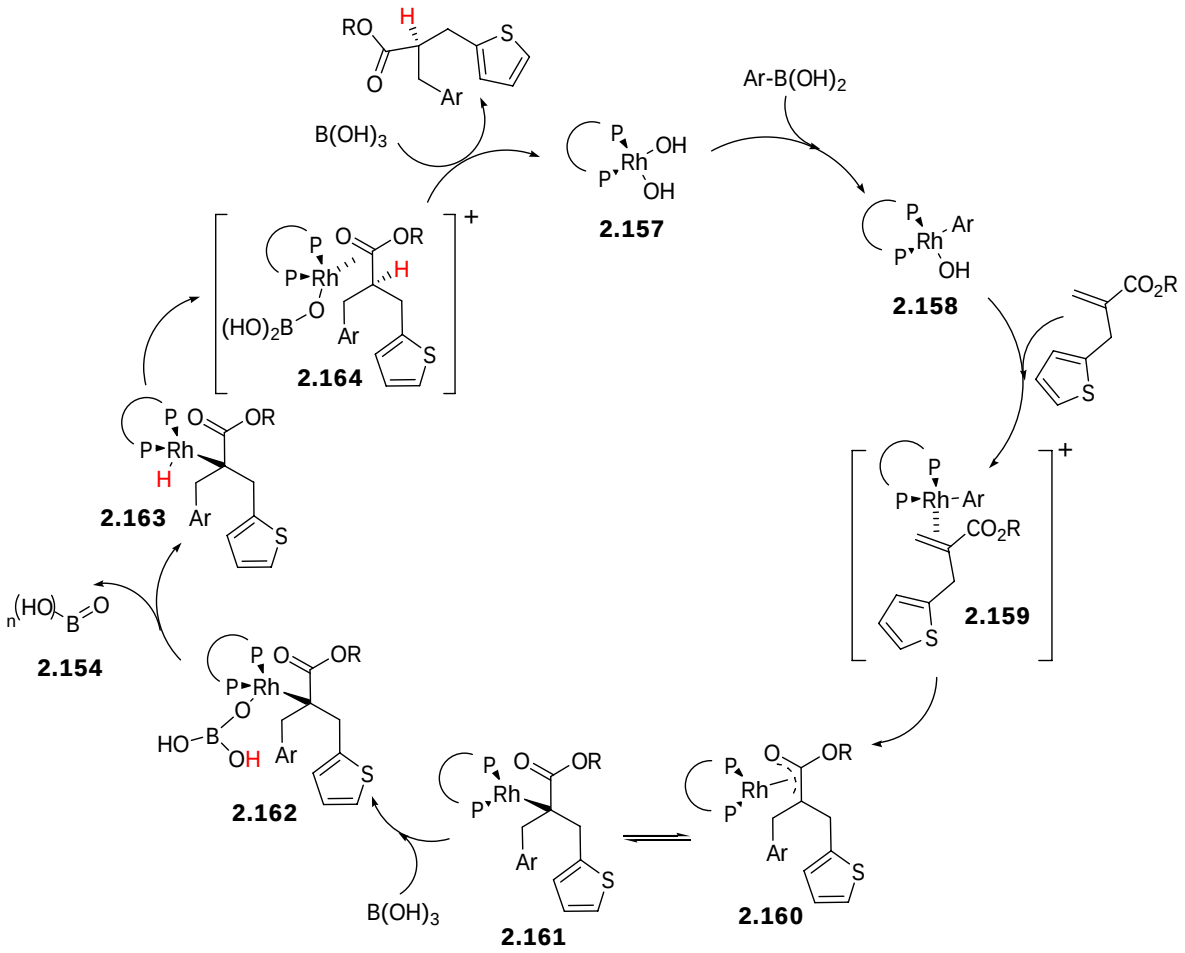
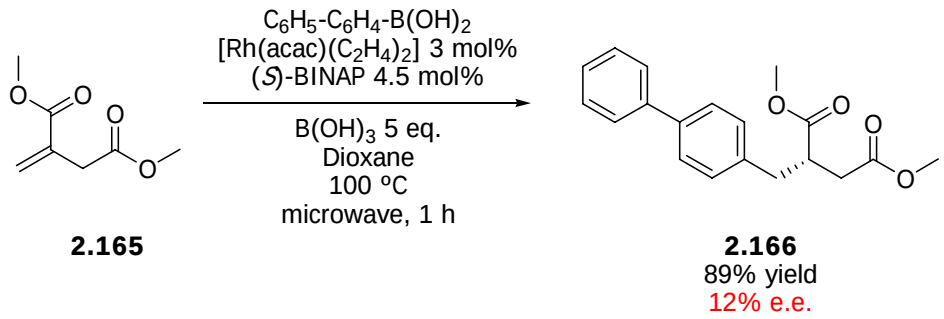


Figure 8

As a final point of interest, the optimised set of conditions was used in the rhodium-catalysed conjugate addition tandem enolate protonation of dimethyl itaconate (**2.165**) to give the corresponding aryl succinic ester (**2.166**). Currently there is still no general methodology for this tandem reaction with optimised conditions for the substrate under examination. Subjecting dimethyl itaconate to 4-biphenyl boronic acid with the standard ligand/catalyst system of [Rh(acac)(C_2H_4)$_2$] and (*S*)-BINAP with boric acid under microwave irradiation for 1 hour gave a quantitative conversion to the desired dimethyl 2-(4-biphenyl) succinate (*Scheme 26*). Unfortunately, upon determining the enantioselectivity of the product only a 12% e.e was observed by HPLC analysis suggesting that use of boric acid as a proton source is ideally suited for benzyl *tert*-butyl acrylate ester substrates. A general protocol for all enolate protonation reactions is yet to be discovered.



Scheme 26

2.7 Conclusion

A new class of 1,1′-alkene substrates with facile formation from aryl and hindered alkyl aldehydes have been successfully screened in rhodium-catalysed tandem addition enolate protonation reactions. Excellent yields and selectivity have been achieved by carefully matching the reaction parameters. The use of microwave chemistry allows the rapid screening of both reaction conditions and subsequent analogue synthesis, giving a possible route to library synthesis of compounds. Boric acid has also proved to be an effective proton source in the reaction either through coordination to the rhodium centre as a pseudo *ortho*-substituted proton source or *via* elimination to a rhodium-hydride species. Studying matched and mismatched acrylate ester and boronic acid permutations has allowed a possible mechanism for the tandem process to be outlined and is in good agreement with data published after this work was completed.[28, 55] To support such a mechanism in the future, DFT computational analysis would be required along with suitable deuterium labelling studies.

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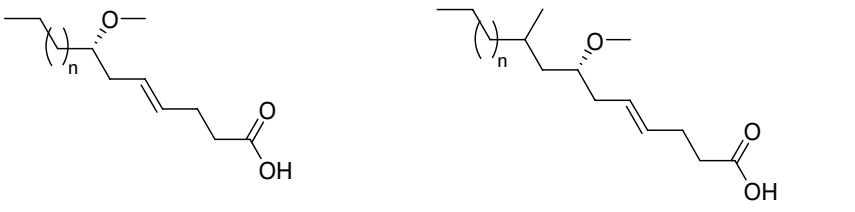
Chapter 3 – Synthesis of Lyngbic Acid & Related Hermitamides *via* 1,4-Addition Reactions with Chiral Boronates

3.1 Objectives

The aim of this chapter is to develop a viable 2-step hydroboration tandem 1,4-addition procedure to give rapid access to the optically pure alkenylated trans fatty acid portion of Malyngamide family of natural products. This reaction will be used to form the major structural building block of Lyngbic acid (**3.1**) leading to a rapid and novel synthesis of the Hermitamides A and B with scope for other analogues.

3.2 Background

Moore and co-workers isolated **3.1** as the major component from the marine cyanophyte *Lyngbya majuscule via* extraction of freeze-dried, shallow-water variety of L. *mujuscula* in 1978.[1] Interest in L. *mujuscula* cyanobacterium stems from its wide abundance in tropical and sub-tropical environments with specimens of the metabolite found in Hawaii,[2, 3] Australia,[4] the Curacao,[5] Asia,[6] and other destinations.[7-9] Lyngbic acid or (4*E*,7*S*)-7-methoxytetradec-4-enoic acid (**3.1**) and its closely related analogue (7*S*)-methoxy-9-methylhexadec-4-(*E*)-enoic (**3.2**) acid have similar physical properties with a 7*S* configuration and a *trans* double bond. The compounds show limited biological activity in a range of studies, but are generally studied due to the ability of closely related cyanobacterial species to give dermatitis-like symptoms in swimmers (*Figure 1*).



3.1
Lyngbic Acid
n= 5

3.2
7-Methoxy-9-methylhexadec-4-(*E*)-enoic acid
n =5

Figure 1

In contrast the Malyngamide natural product family, a range of nitrogen containing lipopeptides derived from amino acid metabolism, have diverse biological activity. It is known

that these natural products have a wide variety of biological properties such as anti-feedant activity[10] to tropical organisms, ichthyotoxicity[9] and cytotoxicity to marine animals.[5, 11, 12] Over 30 examples of Malyngamide natural products (**3.3-3.6**) have been isolated with the amide portion of the compound normally containing an amino acid, lactone, amide, alkaloid or pyrrole functional group.[2, 6, 9, 11-14] This diverse range of functionality in the products gives a number of further subclasses including the Hermitamide (**3.7**) and Isomalyngamide (**3.8**) series of compounds. It is important to note that the 7-methoxytetradec-4-enoic acid (**3.1**) is always present in these materials and has been subject to most scientific interest. The range of diversity also holds the possibility of using Malyngamides for medicinal purposes with serinol based Malyingamides showing anti-HIV potential.[15] Malyngamide *S* (**3.4**) has been assayed for a range of anti-inflammatory, cytotoxicity, and antimicrobial properties. In a separate study Malyngamide *S* also shows inhibited proliferation of human leukemic HL60 cells making it an important synthetic target (*Figure 2*).

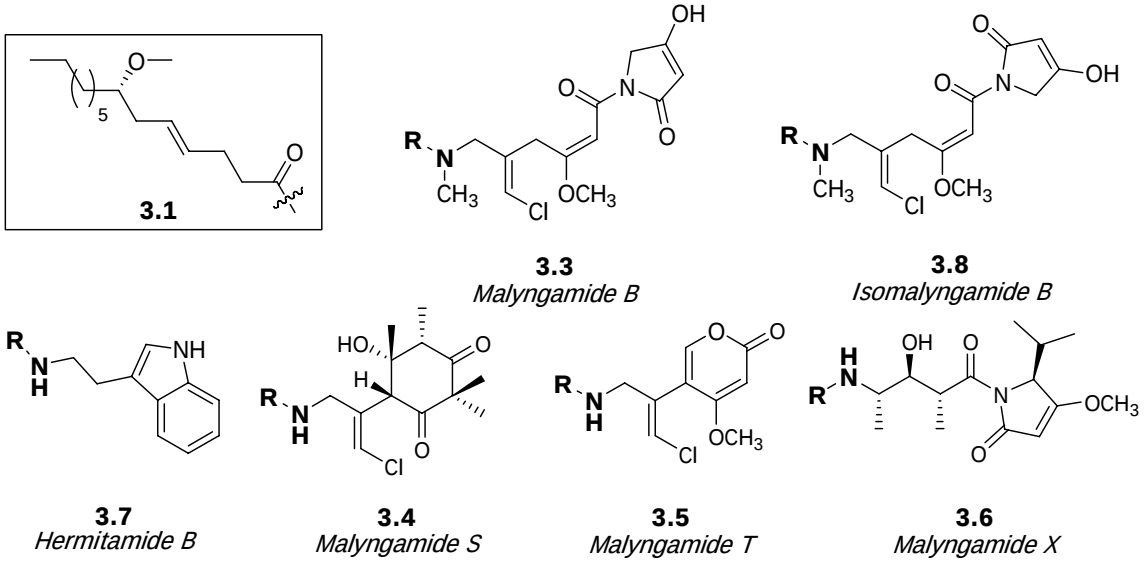
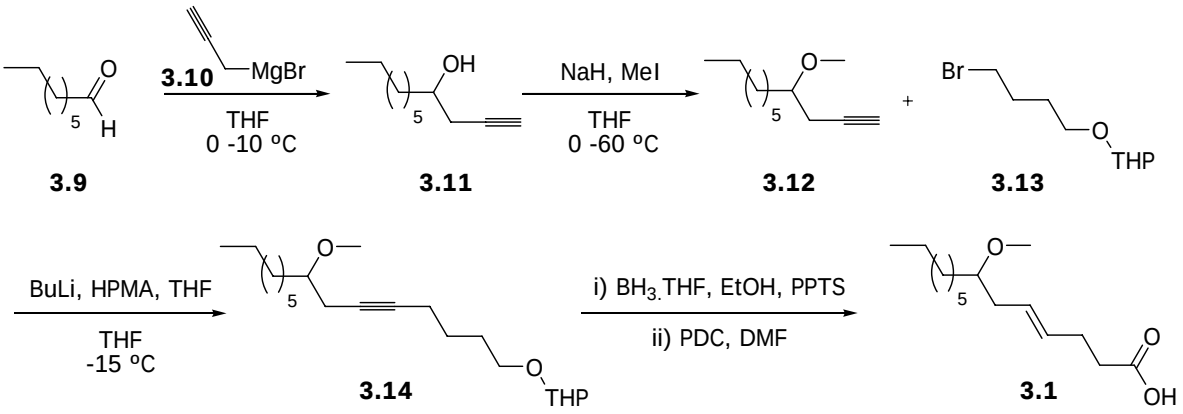


Figure 2

Malyngamide natural products form a large class of marine natural products, but surprisingly only a small number have been undertaken in total synthesis. This has led to continuing research in the field, a number of routes to Lyngbic acid have been previously reported, with a small number of Malyngamides and Hermitamides synthesised more recently.

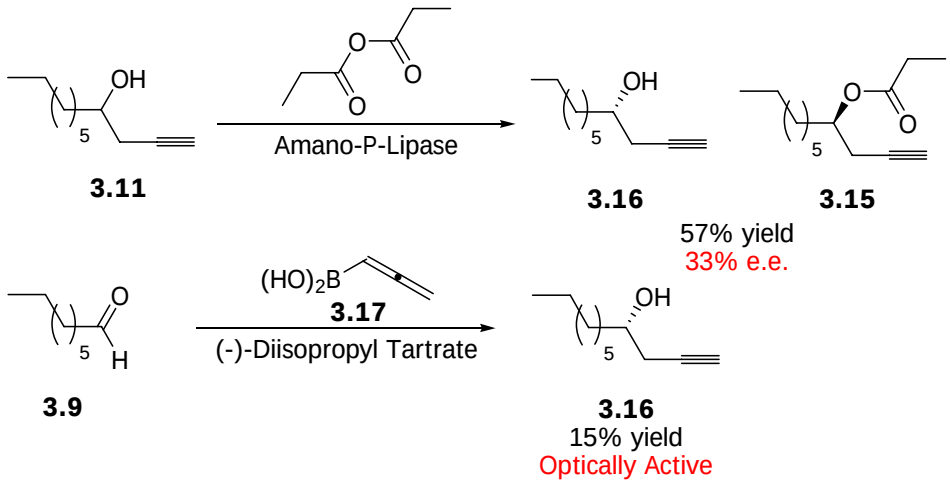
The first total synthesis of racemic Lyngbic acid was achieved in 5 steps by Rybak and co-workers.[16] The group utilised a 1,2-addition strategy to 1-octanal (**3.9**) with propargyl

magnesium bromide (**3.10**) yielding the l-undecyne-4-ol intermediate (**3.11**). Methylation of the alcohol (**3.12**), followed by subsequent addition of the bromo THP protected alcohol (**3.13**) gives the desired alkyne (**3.14**) in 22% yield over 3 steps. Final stages of the synthesis involve hydroboration of the alkyne with borane THF (BH_3.THF) complex to give the (*E*)-alkene, deprotection of the THP group and oxidation of the alcohol to give (±)-**3.1** (Scheme 1).



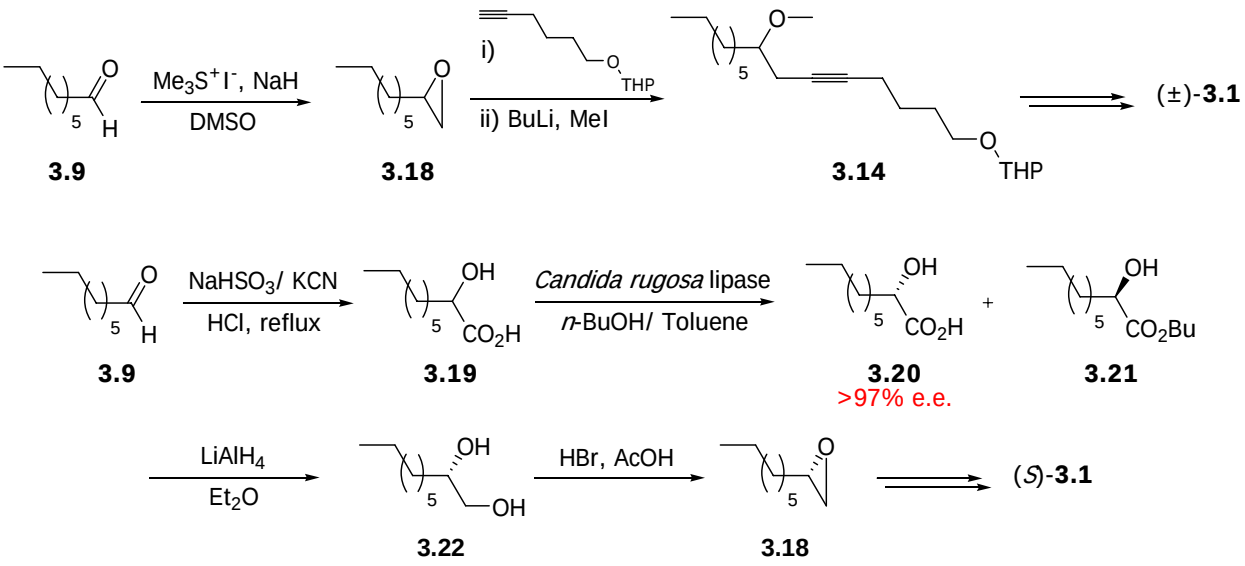
Scheme 1

Rybak *et al* also carried out the first attempt at chiral synthesis of Lyngbic Acid by two differing methods. The approach was the kinetic enrichment of racemic undec-1-yne-4-o1 (**3.11**) to the desired (*S)*-isomer by means of a lipase-catalysed esterification reaction acting predominantly on the undesired isomer. Thus preferential Amano-P lipase-catalysed formation of the propionate ester (**3.15**) from the (*R*)-isomer of racemic alkynyl alcohol gave a 57% yield of the desired (*S*)-alcohol (**3.16**) in 33% e.e. The second route uses a chiral allene boronic ester (**3.17**) as the coupling partner in the 1,2 addition reaction to 1-octanal (**3.9**) which although yielding optically pure material gave a disappointingly low yield of 15% (Scheme 2).



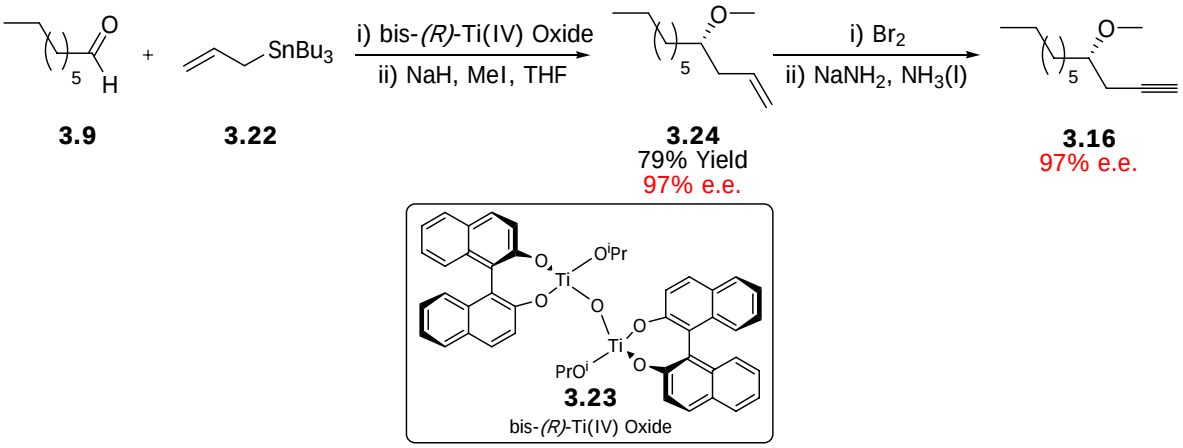
Scheme 2

Enzymatic methods have been used in the seminal synthesis of optically pure Lyngbic acid by Sankaranarayanan and co-workers.[17] The group used α-hydroxy carboxylic acids as the key intermediates in the formation of the chiral epoxide (*S*)-2-heptyloxirane (**3.18**). A lengthy linear procedure was undertaken starting from reaction of 1-octanal (**3.9**) with potassium cyanide yielding the hydroxyl cyano derivative. Acid hydrolysis furnishes the α-hydroxy acid motif (**3.19**) which was subjected to esterification with 1-butanol in toluene using *Candida rugosa* lipase (CRL) as the catalyst. In the presence of freshly activated 4Å molecular sieve powder, the reaction proceeded smoothly to furnish the (*S*)-α-hydroxy carboxylic acid (**3.20**) and (*R*)-butyrate ester (**3.21**) in optically pure form. To complete the 11 step synthesis the carboxylic acid is reduced with lithium aluminium hydride to the enantiopure diol (**3.22**) followed by selective bromination and Payne-type rearrangement to furnish the chiral epoxide (**3.18**). Final steps to the final product included ring opening of the epoxide with the appropriate acetylide species followed by a similar hydroboration, deprotection, and oxidation sequence comparable to previous reports by Rybak (Scheme 3).[16]



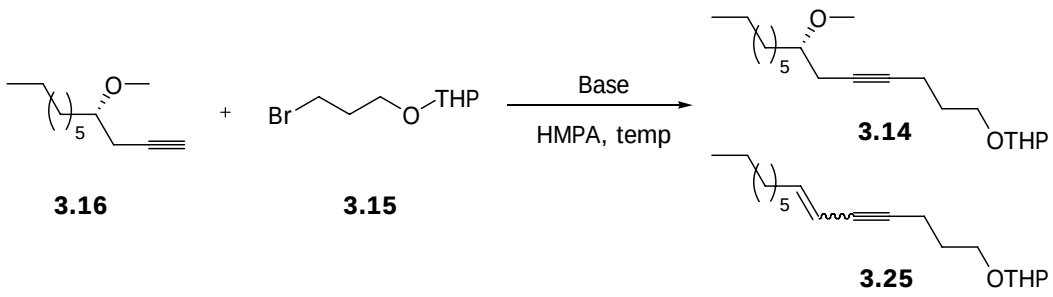
Scheme 3

The ideal solution for forming the chiral alcohol motif is the asymmetric addition of organometallic reagents to the corresponding aldehyde. The area of catalytic enantioselective allylations to carbonyl compounds has become an extremely efficient method of forming chiral allylic alcohols.[18] One of the most extensively studied asymmetric allylation reactions employs BINOL as the chiral environment, with a Ti(IV) Lewis acid as the metal catalyst. This approach has been utilised by Li and co-workers in their synthesis of *(4E,7S)*-(–)-7-methoxydodec-4-enoic acid.[19] The asymmetric allylation of 1-octanal (**3.9**) with allyl tributyltin (**3.22**) is catalysed by an *in-situ* generation of a chiral Ti(IV) BINOL catalyst (**3.23**). This gives the desired (*S*)-4-hydroxy-1-nonene (**3.24**) intermediate as a single component in 79% yield and 97% e.e. The allylic alcohol can be readily converted to the terminal alkyne *via* bromination and dehydrobromination giving the desired alkyne product (**3.25**) in 73% yield (Scheme 4).



Scheme 4

The alkyne could be formed as optically pure material, but there were complications with the subsequent coupling of 2-(3-bromopropoxy)-tetrahydro-2H-pyran (**3.15**). It was found that the reaction did not proceed to completion under previously described conditions, with the methoxy group undergoing elimination to give an ene-enyne (**3.25**) side product. After screening a range of bases and temperatures it was found that *t*-BuLi gave the best compromise between reactivity and steric bulk. Using this system 82% yield of the allylic methyl ether (**3.14**) was obtained, with the elimination product easily separated by column chromatography (Table 1). Stereoselective synthesis of (4*E*,7*S*)-(–)-7-methoxydodec-4-enoic acid in eight steps from 1-octanal is the most common route to Lyngbic acid. The reaction provides highly enantiopure quantities of *(S)*-4-hydroxy-1-nonene intermediate on a reproducible 500 mg scale.[19, 20]

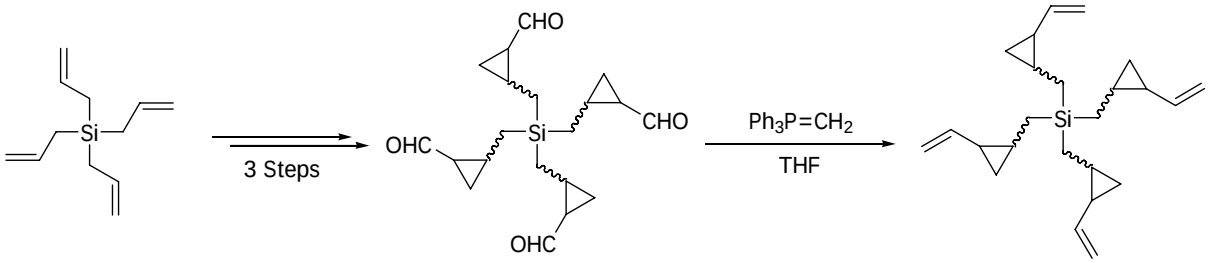


3.16 **3.15** **3.14** **3.25**

Entry	Conditions	Temperature (ºC)	% **3.14**	% **3.25**
1	*n*-BuLi, –84 °C (1 h), then r.t. (2 h)	-84		75
2	LDA, –20 °C (1 h)	-45	-	-
3	$LiNH_2$, –30 °C (30 min)	-30		82
4	*t*-BuLi, 0 °C (1 h)	0	70	5

Table 1

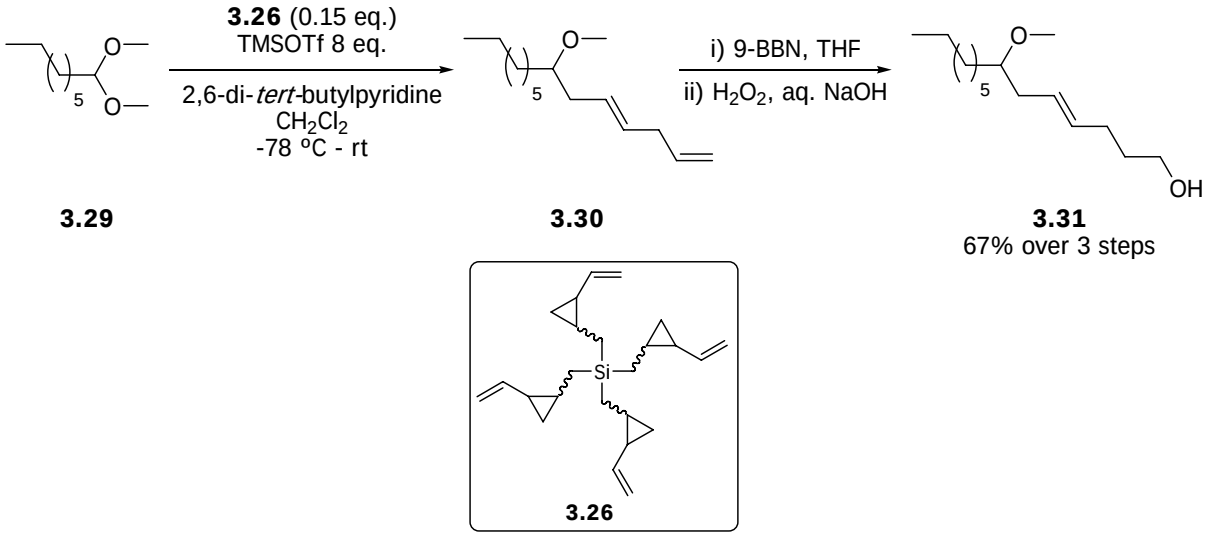
One final synthesis of note is the use of a "skipped diene" strategy as proposed by Braddock *et al.*[21] The group has shown that cyclopropylvinylsilane reagents (**3.26**) undergo stereocontrolled Prins-reactions with activated acetals giving exclusive *E*-olefin selectivity. The synthesis of the key cyclopropylvinylsilane reagent is achieved from the corresponding tetra-allylic silane reagent (**3.27**), which is cyclopropanated by sequential treatment with EDA under copper(I) catalysis. The tetra-cyclopropane intermediate is reduced to the tetra-cyclopropanyl alcohol and then oxidised to the tetra-aldehyde (**3.28**) using Dess-Martin periodinane. Finally global Wittig methenylation gave the desired silane (**3.26**) as a mixture of 8 major and 6 minor isomers with a 45% *Z* to 55% *E* ratio of alkene resonances by ^{1}H NMR spectroscopy. Fortunately for further chemical transformations the range of isomers is unimportant as each vinyl moiety transfers its group independently under stereoelectronic control to give *E*-skipped dienes (Scheme 5).



3.27 **3.28** **3.26**
21% over 5 steps
45:55% *Z:E*

Scheme 5

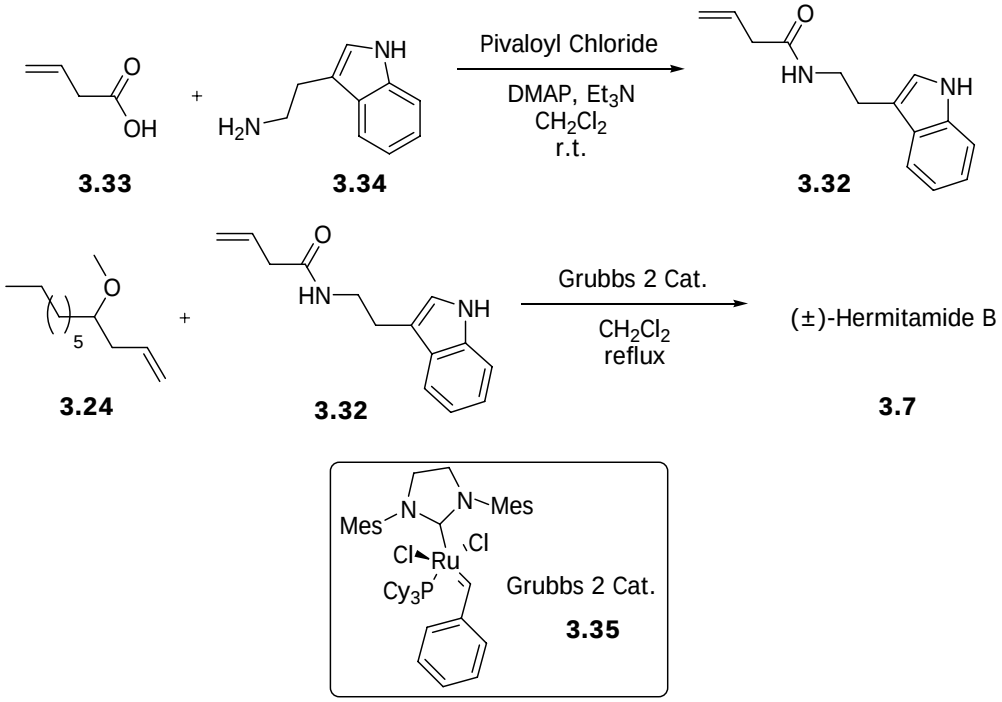
Using the newly formed reagent **3.26**, rapid formation of (±)-Lyngbic acid can be achieved in 3 steps utilising a cyclopropylmethylsilane-terminated Prins reaction. Using 1,1-dimethoxyoctane (**3.29**) as the substrate, Prins reaction of tetravinylsilane mediated by Lewis acid trimethylsilyltriflate (TMSOTf) afforded the skipped diene methyl ether (**3.30**) in 67% yield with exclusive *trans* geometry in the central alkene. Selective hydroboration of the terminal alkene with 9-BBN followed by alkaline hydrogen peroxide work-up gave the primary alcohol (**3.31**), which could be readily oxidised to the corresponding carboxylic acid using PDC in DMF. Through this process the construction of the complete carbon skeleton is realised in a single step introducing the C7-methoxy group with complete control of 4*E*-olefin geometry Currently this is the shortest overall route to (±)-Lyngbic acid to date, although the cyclopropylsilane reagent adds a number of steps to the overall synthesis (Scheme 6).



Scheme 6

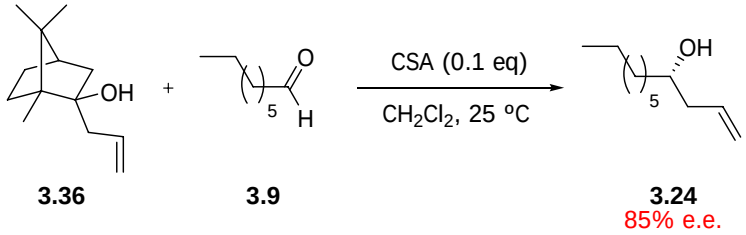
Synthesis of Hermitamide A and B along with Malyingamide substrates has received far less attention. The first formal total synthesis of Hermitamides A and B was achieved by Virolleaud and co-workers in 2006.[22] The group used a cross-metathesis approach to form the carbon skeleton of Hermitamide A and B. Initial steps to form the amide motif (**3.32**) involve the formation of the acid chloride from but-3-enoic acid (**3.33**) and subsequent coupling with tryptamine (**3.34**) or phenyl ethylamine in dichloromethane at room temperature. The key 4-hydroxy-1-nonene derivative (**3.24**) is prepared by similar methods to Li,[19, 20] using allyl magnesium bromide instead of the respective tributyl stannane reagent. This is then coupled to the amide motif by standard cross-metathesis methods with Grubbs

second generation ruthenium catalyst (**3.35**) in refluxing dichloromethane. The final ruthenium cross-metathesis reaction gives both Hermitamide A and Hermitamide B (**3.7**) in racemic form in satisfactory yields (Scheme 7).



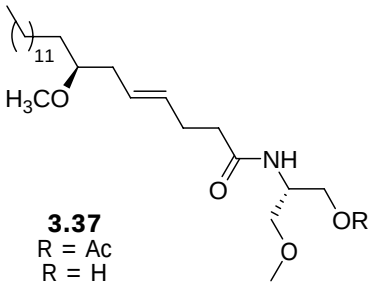
Scheme 7

In order to form the chiral allylic alcohol the methods of Loh *et al* followed exploring the reactivity of a (+)-camphor derived homoallylic alcohol auxiliary (**3.36**).[23, 24] Octanal (**3.9**) is reacted with 1 equivalent of the auxiliary with catalytic camphorsulfonic acid (CSA) in dichloromethane at room temperature giving the desired homoallylic alcohol in 85% e.e. This route gives a large scale synthesis of (*S*)-4-hydroxy-1-nonene (**3.24**) yielding over 2 grams of the enantioenriched material. Surprisingly the alcohol formed was not derivatised and used in the formation of Hermitamide A and B, possibly due to five equivalents of the methoxy nonene required giving smooth cross-metathesis coupling with the alkenyl amide (Scheme 8).



Scheme 8

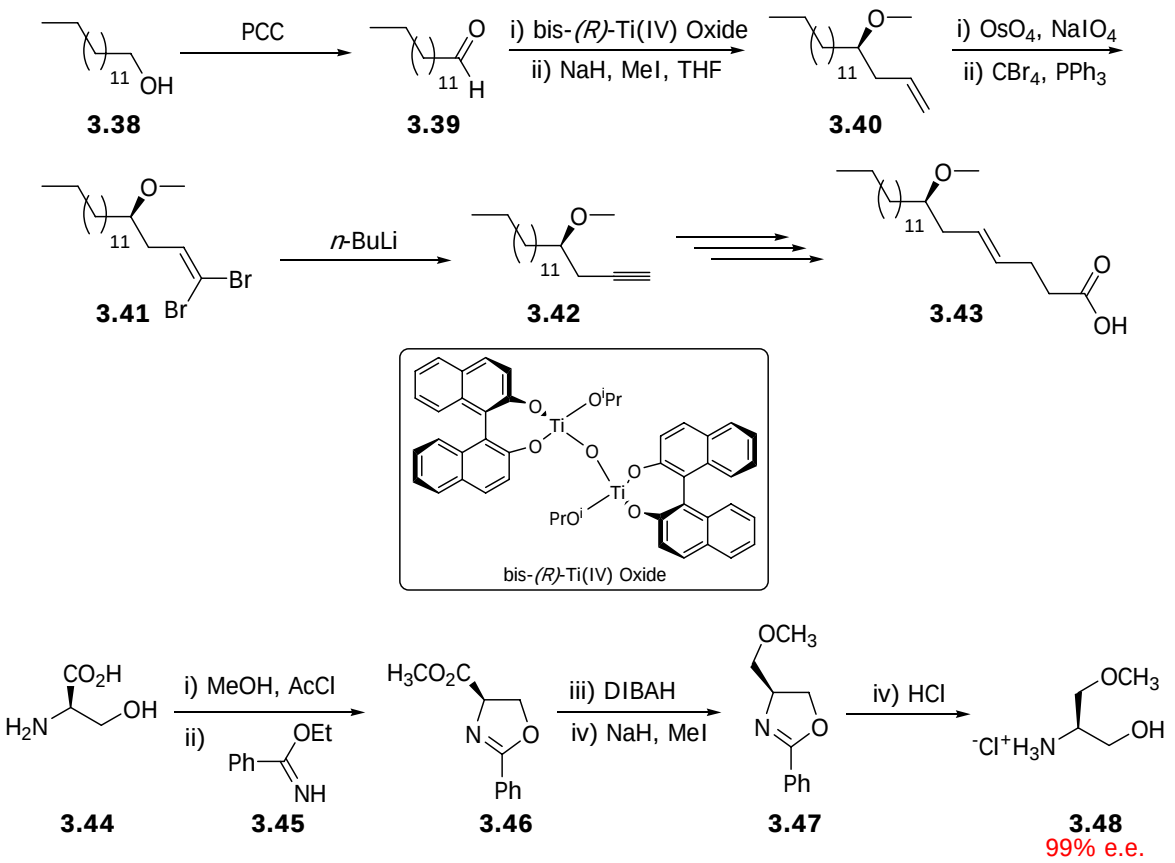
Malyngamide structures based on β-amino alcohol serinol (**3.37**) have been shown to display weak anti-HIV activity.[4] Such Malyngamides structures were isolated from algae in the mouth of the King George River in north-western Australia. The amides have been classified as Malyngamides due to their fatty acid component, but their amide moiety, serinol, is simpler than the amine moiety of previously described in other Malyngamide scaffolds. The compound displays two unique features; the first is the (7*R*)-methoxy group previously unobserved in other similar structures as well as a serinol amino alcohol side chain (Figure 3).



3.37
R = Ac
R = H

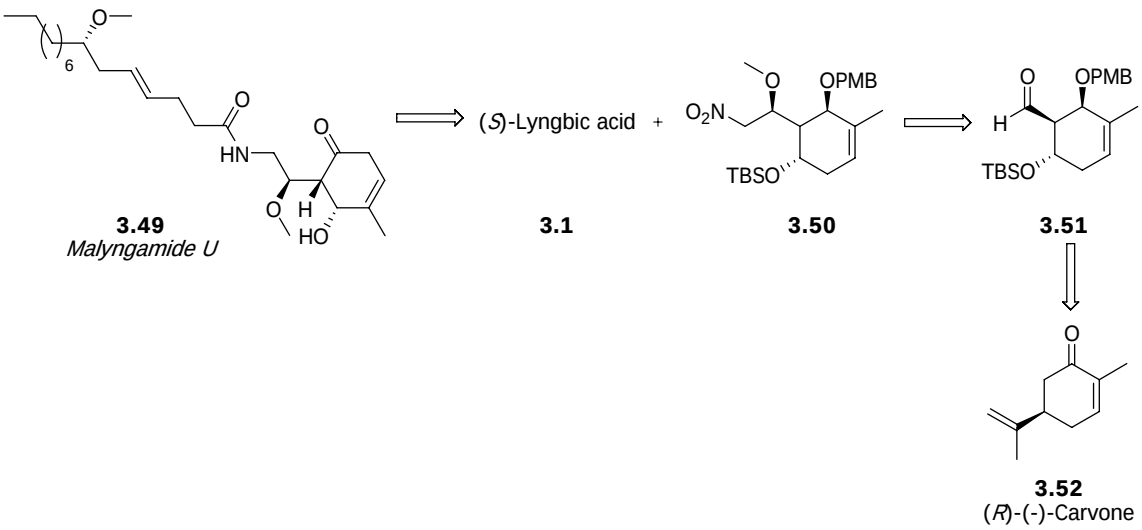
Figure 3

The first reported total synthesis of serinol-derived malyngamides was achieved by Chen and co-workers.[15] The proposed route uses tetradecan-1-ol (**3.38**), which was oxidised to the corresponding aldehyde (**3.39**) using pyridinium chlorochromate (PCC). The key stereogenic centre (**3.40**) was constructed by catalytic asymmetric allylation reaction as previously reported. The alkene formed was oxidised to the aldehyde, which was used in a Corey-Fuchs reaction giving the *gem*-dibromo compound (**3.41**). Treatment of this species with butyl lithium gives the desired terminal alkyne product (**3.42**). Standard procedures allow access to the epimeric fatty acids (**3.43**) with the structural features of (*4E,7S*)-7-methoxytetradec-4-enoic acid. The serinol side chain and its epimer were derived from previous routes described by Meyers *et al*.[25] Starting from widely available amino acid *D*-serine (**3.44**), esterification to the methyl ester followed by reaction with ethyl benzimidate (**3.45**) gave the desired oxazoline auxillary (**3.46**) in 90% yield over two steps. Diisobutylaluminum hydride (DIBAL) reduction of oxazoline produced alcohol in greater than 90% yield. Alkylation of the alcohol with sodium hydride and methyl iodide provides the methoxy ether derivative (**3.47**). The final step involves auxiliary cleavage by heating in 4M hydrochloric acid yielding the desired methoxy serinol (**3.48**) in enantiopure form. The two products are then coupled *via* DCC coupling to give the final Malyngamide natural products in greater than 97% e.e. (Scheme 9).



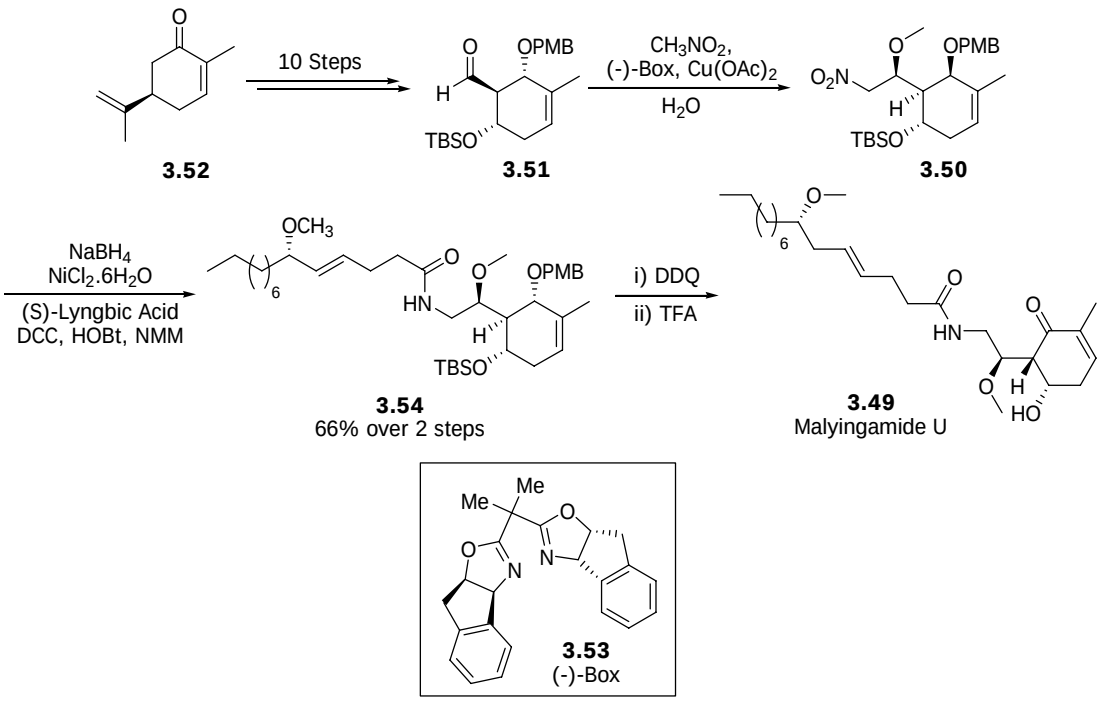
Scheme 9

A more complex natural product synthesis is the enantioselective formation of Malyngamide U (**3.49**) by Li and co-workers.[20] Reterosynthesis of the product leads to Lyngbic acid (**1**) and a nitro compound (**3.50**) that is prepared by Henry reaction from the corresponding chiral aldehyde (**3.51**). In turn the highly substituted cyclohexenone can be formed from chiral pool reagent (*R*)-(-)-carvone (**3.52**) (Scheme 10).



Scheme 10

The Lyngbic acid section of the molecule was prepared by previous literature means and has been previously discussed.[15, 19] The amide moiety is a challenging piece of synthesis requiring 13 steps to reach the key chiral aldehyde. For the asymmetric Henry reaction, Evans' copper acetatebis(oxazoline) catalyst (-)-Box (**3.53**) was reported to give high diastereoselectivities and yields for aliphatic aldehydes.[26, 27] Use of this catalyst system led to the desired nitro-alcohol (**3.50**) with high diastereoselectivity (60:1) in 68% yield on the basis of 37% conversion. In addition to this the diastereomers could be separated by careful chromatography on silica gel. Reduction of the nitro group was achieved with sodium borohydride, although the corresponding amine was found to be unstable. Therefore an *in situ* reduction followed by DCC coupling with Lyngbic Acid was used to complete the carbon scaffold of the compound (**3.54**). Oxidation of the *para* methoxybenzyl (PMB) protected alcohol with dichlorodicyanoquinone (DDQ) leads to the TBS protected cyclohexenone motif. Final deprotection of the TBS group with TFA gave the completed Malyngamide U natural product (**3.49**) in 18 steps in an overall yield of 3% from (*R*)-(-)-carvone (Scheme 11).



Scheme 11

The final total synthesis of Maylngamide natural products is that of Malyngamide *X* (**3.55**) by Isobe *et al*.[28] This Malyngamide contains the first isolated (7*R*)-Lyngbic acid side chain and is also connected to a novel tripeptide backbone. The compound was isolated from the Thai sea hare *Bursatella leachii*, with the gross structure established on the basis of mass spectroscopic data with 1D and 2D NMR.[6] Malyngamide *X* can be retrosynthetically divided into four building blocks; (*4E,7R*)-(+)-7-methoxytetradec-4-enonic acid (**3.56**), the epimer of Lygbic acid, two amino acid residues generated from N-methyl-*L*-alanine (**3.57**) and Boc-*L*-alanine methyl ester (**3.58**), respectively. Finally the right side pyrrolidone segment (**3.59**) is derived from Boc-*L*-valine (**3.60**), Meldrum's acid (**3.61**) and propionyl chloride (**3.62**) (Figure 4).

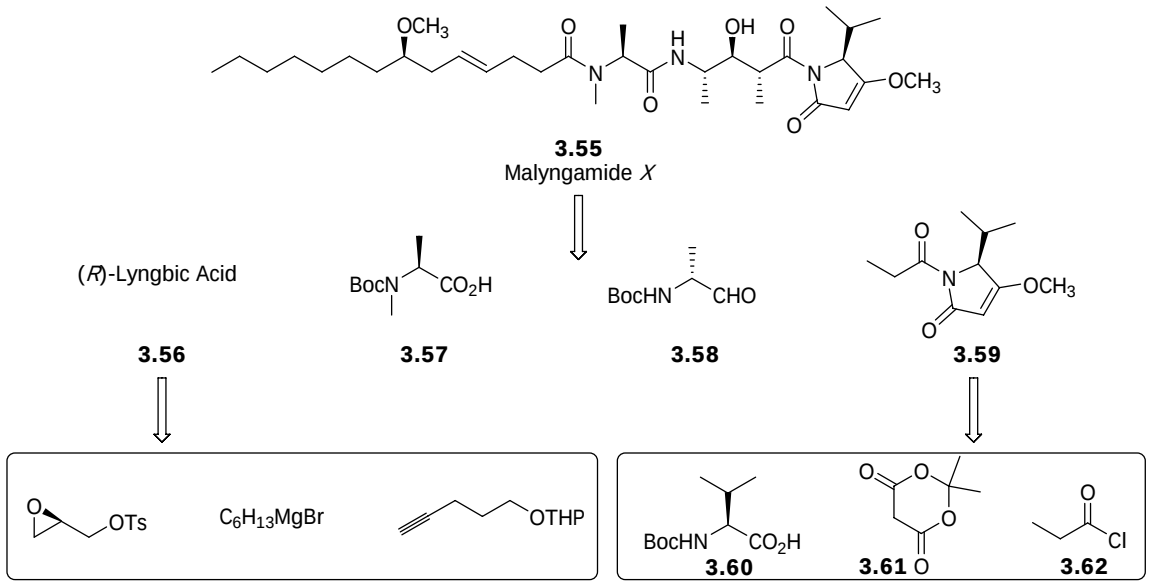
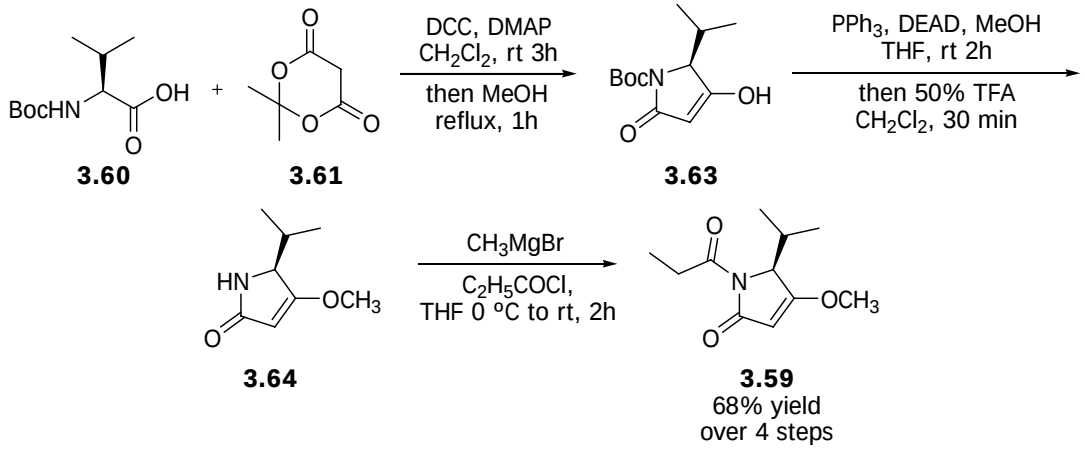


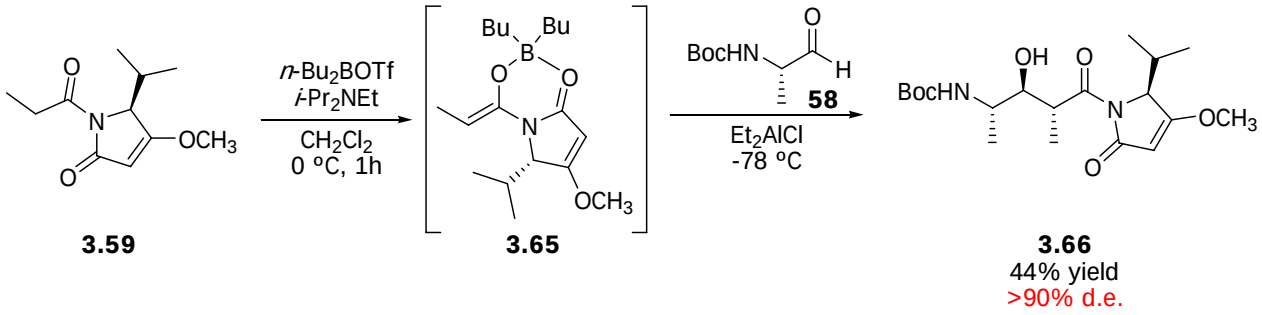
Figure 4

Routes to the (7*R*)-Lyngbic acid side chain have been previously discussed are and not detailed further.[19] The pyrrolidone core is formed by initial DCC coupling of Meldrum's Acid (**3.61**) with *N*-Boc valine (**3.60**) followed by evaporation of solvent and subsequent refluxing in methanol to generate the *N*-Boc protected pyrrolidone derivative (**3.63**). This was then reacted under Mitsunobu conditions with methanol to form the corresponding methyl ether as a single stereoisomer. Removal of the Boc-protecting group with TFA provided the desired amide (**3.64**) which was deprotonated with methyl magnesium bromide in THF at 0 ºC. Alkylation of the amide anion with propionyl chloride and warming of the reaction mixture to room temperature gave *N*-propionyl pyrrolidone (**3.59**), the key intermediate for the subsequent stereoselective aldol reaction (Scheme 12).



Scheme 12

The starting material, imide pyrrolidone (**3.59**) containing a chiral isopropyl group, was converted into the (*Z*)-imide enolate (**3.65**) by treatment with n-Bu_2BOTf and Hunig's base at 0 ºC in CH_2Cl_2 for 1 h. Lewis acid catalysts were studied in the *anti*-aldol reaction with diethylaluminium chloride (Et_2AlCl) mediated coupling proving most effective, thus exposure of *N*-Boc-L-alaninal (**3.58**) with Et_2AlCl at -78 ºC for 5 h, generated *anti*-aldol product (**3.66**) in 44% yield with >90% d.e. setting up two new stereogenic centres in pyrrolidone derivative. Final steps in completing the synthesis involve peptide coupling with deprotection of the relevant protecting groups followed by coupling reactions to give the tripeptide segment. The Malyngamide X scaffold was accomplished by stirring epimeric Lyngbic acid with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC.HCl–HOAt) and Hunig's base at room temperature for 18 h to give final product in 44% yield for the final step (Scheme 13).



Scheme 13

In conclusion marine natural products from L. *mujuscula* cyanobacteria have provided a wide-ranging and diverse set of products for chemical synthesis. Only a small range of these products has been successfully accomplished by total synthesis, and new routes to Lyngbic acid are still required. It would be desirable to produce Lyngbic acid on larger scales giving greater access to multigram quantities of Malyngamide scaffolds for medicinal product assays.

3.3 Initial Studies

The ability to undertake multiple reactions in a single reaction vessel presents a number of opportunities for the synthetic organic chemist to improve chemical transformations. Single catalysts performing multiple processes often circumvent the time-intensive and yield-reducing isolation and purification steps of synthetic intermediates in multiple-step syntheses. This is especially true in the addition of alkenyl organoboranes to enones where preparation and purification of the organometallic fragment can be time consuming and require air sensitive techniques to manipulate.

The initial concept involves the retrosynthesis of Hermitamide A (**3.67**) and B (**3.7**) to synthons that could be used in our previously developed rhodium-catalysed conjugate addition methodology. In order to further developments in tandem processes, the chiral alkyne derivative (**3.16**) was required to attempt a 1-pot synthesis of Hermitamides A and B. The keys steps are hydroboration, conjugate addition and racemic protonation leading to rapid access to Lyngbic acid derived products and possible analogues. Hayashi and co-workers have undertaken 1-pot hydroboration rhodium-catalysed conjugate addition using 2-alkenyl-l,3,2-benzodioxaboroles derived from the corresponding terminal alkynes and catecholborane giving products in up to 90% yield and 98% e.e.[29] Similar hydrometallation reactions have been achieved with organostannane and organosilcon reagents with comparable success.[30-32]

It was decided that a route derived from an enantiopure epoxide (**3.18**) would be a good starting material for further transformations. Regioselective ring opening with a suitable metal acetylide complex (**3.68**) would provide the desired propargyl alcohol which could be suitably protected or directly methylated to give the (*S*)-4-methoxyundec-1-yne intermediate (**3.12**). The amide right hand side of the molecule could be synthesised *via* acryloyl chloride (**3.69**) and the corresponding amine such as phenylethylamine (**3.70**) or tryptamine (**3.34**) respectively. A coupling reaction of these α,β unsaturated amides (**3.71, 3.72**) with an *in-situ* generated organometallic species would give the complete natural product scaffold with complete control of the *(E)* geometry of the alkene. Removing all of the coupling procedures and protecting group strategy should lead to the shortest synthetic route to the Hermitamide natural product family. In addition, from all literature searches this would be the first example

of a chiral organometallic reagent being used in a rhodium-catalysed reaction procedure. The major advantage of this route is the ability to synthesise large quantities of the desired fatty acid motif in an efficient manner which has yet to be achieved. Although Lewis acid catalysed allylation has proved to be a popular method of forming the chiral methoxy group it still has the disadvantages of the titanium-catalyst being highly air and water sensitive, as well as requiring 4-5 further steps to synthesise Lyngbic acid before subsequent amide coupling (Figure 5).

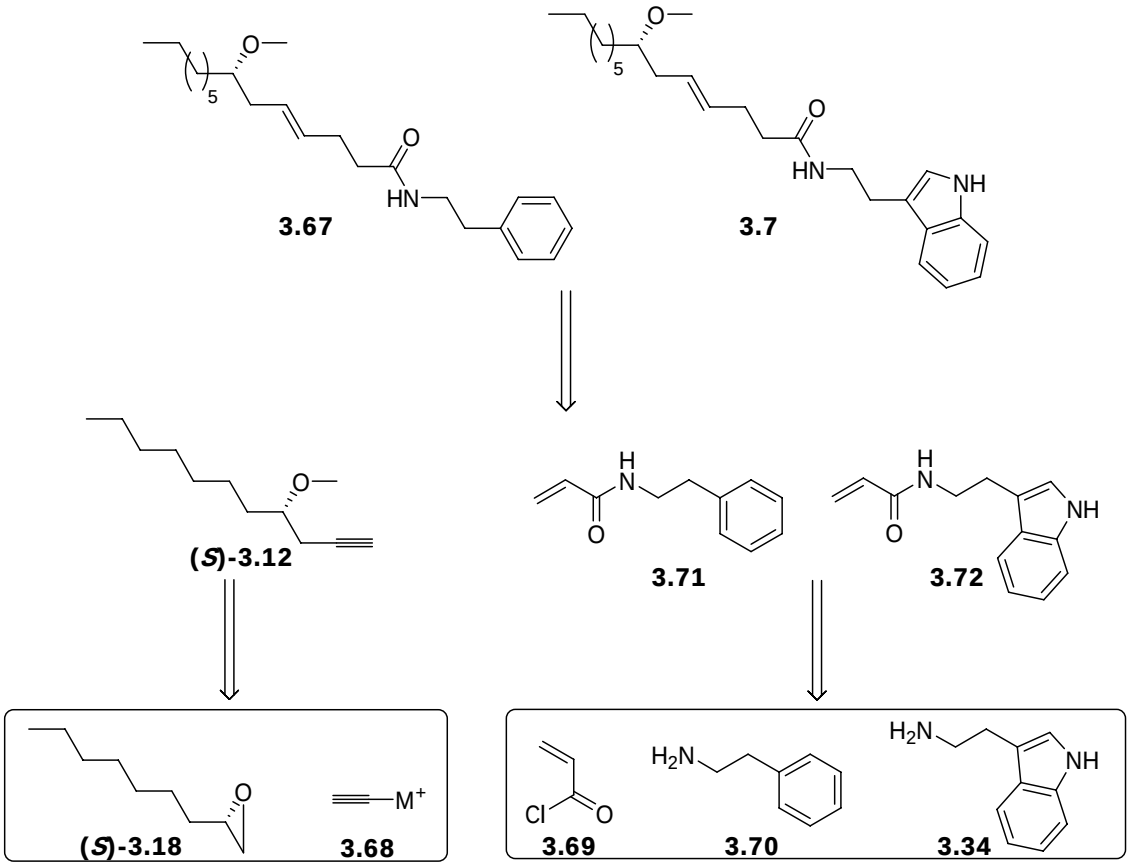
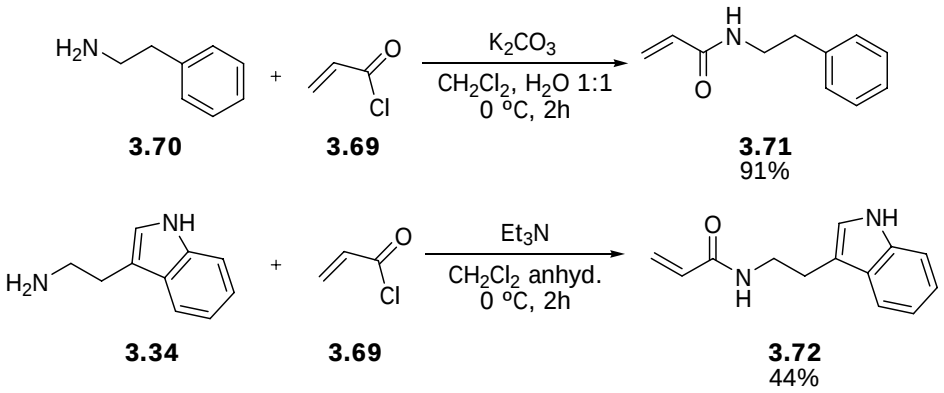


Figure 3

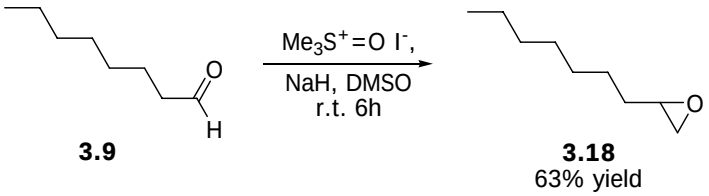
Initial studies involve the formation of the acrylamide portion of Hermitamides A and B; these reagents should be suitable for rhodium-catalysed conjugate addition reactions. Both phenylethylamine and tryptamine acrylamide (**3.72, 3.73**) can readily be prepared by direct reaction with acryloyl chloride (**3.69**) and a suitable base.[33] Initial routes involved a biphasic system utilising aqueous potassium carbonate. Phenylethylamine (**3.70**) was dissolved in dichloromethane and to this was added an aqueous solution of K_2CO_3 with vigorous stirring. A solution of acryloyl chloride (**3.69**) in dichloromethane was added at 0 ºC and reaction

mixture allowed to warm to ambient temperature over 2 hours. Upon filtration and removal of solvent the phenylethylamine acrylamide (**3.71**) was isolated in 91% yield. The acrylamide based on tryptamine (**3.34**) was not readily prepared using these conditions and gave an impure mixture of products. To this end a route using anhydrous triethylamine as base gave the final product (**3.72**) in 44% yield after flash column chromatography. For further natural product synthesis this route allows the amide portion of the molecule to be synthesised quickly and effectively. Addition of acryloyl chloride to any suitable amine would lead to quick assembly of a range of novel structures based on the Malyngamide scaffold (Scheme 14). This was seen as a positive area of development towards similar structures based on amino acids and amino alcohols previously discussed.



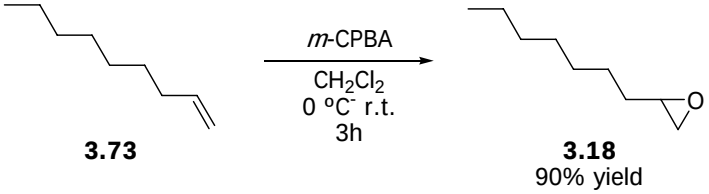
Scheme 14

The other target molecule to complete the total synthesis is the (*S*)-4-methoxyundec-1-yne derivative. The appropriate epoxide 2-heptyloxirane (**3.18**) was unavailable commercially so standard synthetic routes were undertaken. The initial reaction involved Corey-Chaykovsky method employing 1-octanal (**3.9**) and trimethylsulfonium iodide.[34] Sodium hydride was dissolved in anhydrous DMSO and cooled to 0 ºC, a trimethylsulfonium iodide solution in anhydrous DMSO was added dropwise to form the corresponding methylsulfinyl carbanion. Finally a solution of 1-octanal (**3.9**) was added over 30 minutes and the reaction warmed to 60 ºC for 4 hours. Upon aqueous extraction the desired epoxide (**3.18**) was formed in 63% yield with greater than 98% purity. Although this reaction was achieved on a 25 g scale the yields were always modest and, for optimum purity, distillation of the compound had to be undertaken, further lowering the yield (Scheme 15).



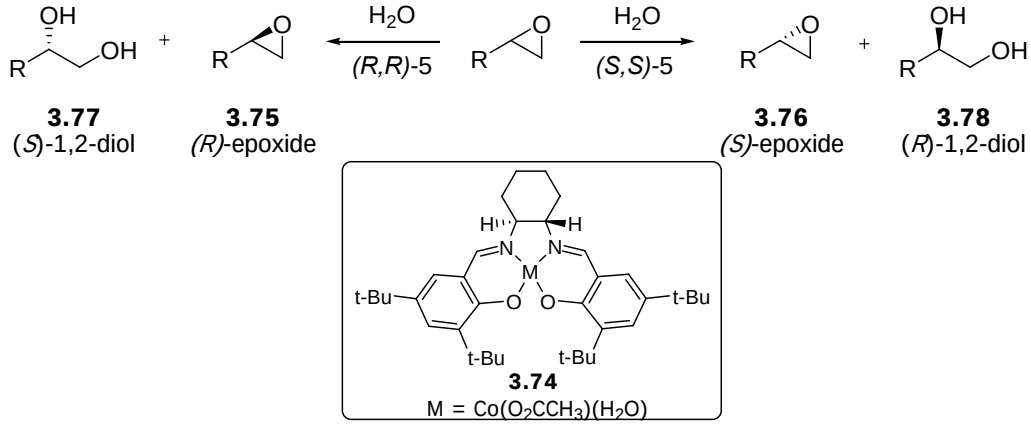
Scheme 15

The chosen route was *meta*-chloroperbenzoic acid (*m*-CPBA) epoxidation of 1-nonene (**3.73**), which was dissolved in dichloromethane and cooled to 0 ºC under nitrogen. To this was added a filtered solution of 75% *m*-CPBA in DCM keeping the internal temperature of the flask at 4 ºC. The solution was brought up to ambient temperature and stirred for 3 hours. After quenching the solution with potassium thiosulfate and sodium bicarbonate the extracted layers were concentrated. All solid impurities and residual *meta*-chlorobenzoic acid were filtered and washed with hexane to yield pure 2-heptyloxirane without the need for column chromatography or distillation. Following this route 25 g of >96% pure epoxide (**3.18**) could be rapidly prepared for further transformations (Scheme 16).



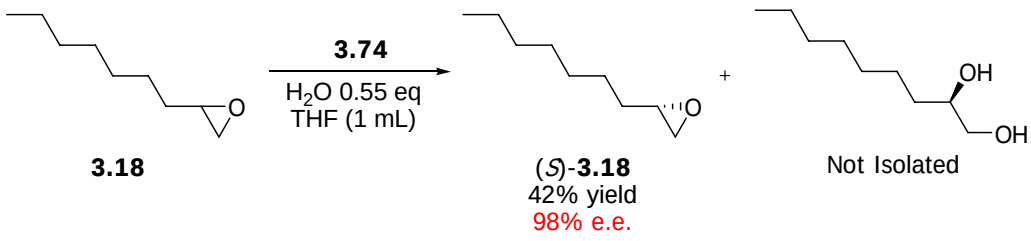
Scheme 16

For the synthesis of the chiral epoxide the chemistry of Jacobsen and co-workers was undertaken.[35-37] Hydrolytic kinetic resolution has proved to be an efficient and consistent method of forming enantiopure chiral epoxides and diols. This approach allows a range of epoxides to be successfully resolved and remains one of the most widely used asymmetric transformations in industrial scale processes to date. Both chiral cobalt-salen complex precursors (**3.74**) to the reaction are inexpensive and widely available and the corresponding reactions are very reliable often giving the chiral epoxide (**3.75, 3.76**) and 1,2-diol (**77, 78**) products in over 95% enantiomeric excess (Scheme 17).



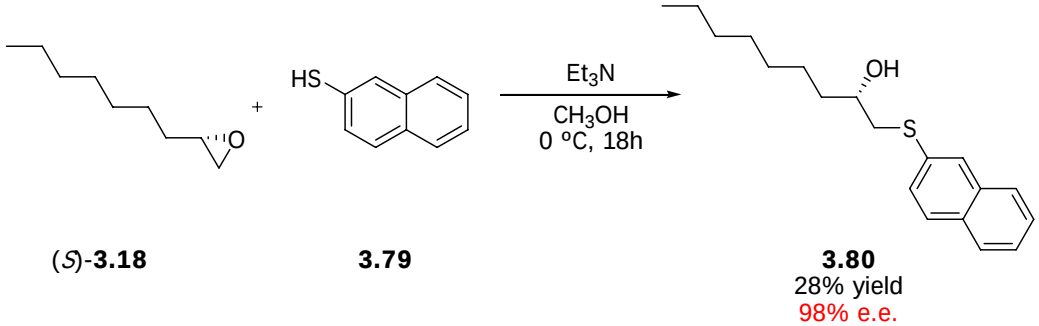
Scheme 17

With the knowledge that aliphatic long chain epoxides are exceptional substrates for hydrolytic kinetic resolution often giving close to 50% of the maximum possible yield and greater than 95% e.e. it was envisaged that a large quantity of chiral material could be prepared. The experimental procedure first used by Jacobsen was followed.[36] The chiral cobalt-salen ligand complex was formed by stirring the commercial precursor N,N'-bis(salicylidene)ethylenediaminocobalt(II) (**3.74**) in air with acetic acid for 1 hour. The dark brown solid remaining after removal of solvent was resuspended in neat epoxide (**3.18**) and cooled to 0 ºC and water (0.55 eq.) was added dropwise and stirred for 72 hours at ambient temperature. The crude reaction mixture was then distilled from the catalyst and diol products at low vacuum (60 ºC, 4 mmHg) to give the chiral epoxide ((*S*)-**3.18**) product as a colourless oil in 42% yield. Initially problems with isolation of product and selectivity were observed, due to the turbidness of the crude reaction mixture leading to incomplete catalysis. This was rectified by addition of a small quantity of anhydrous solvent to the mixture such as tetrahydrofuran or isopropanol to give a more homogeneous reaction environment (Scheme 18).

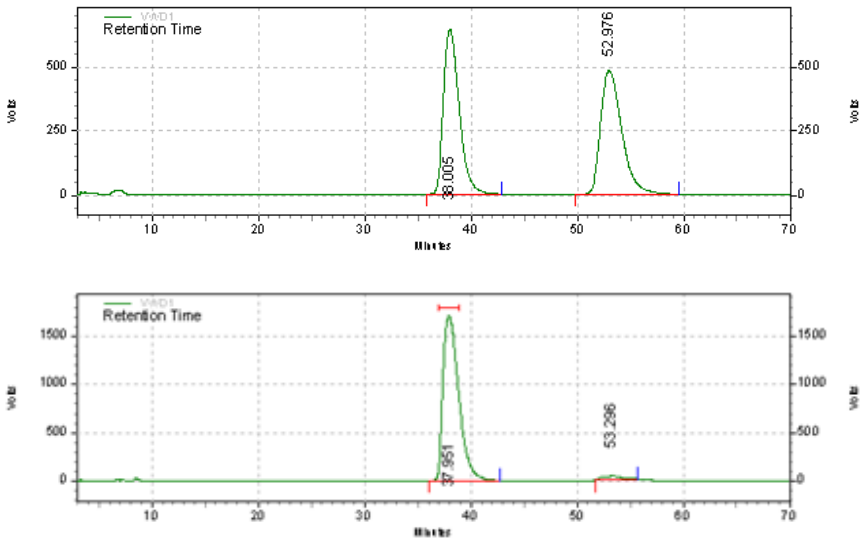


Scheme 18

Analysis of the enantioselectivity was achieved by comparison with literature optical rotations for (*S*)-2-heptyloxirane $[\alpha]_D^{24}$ = -8.67 (c = 1.04, CH_2Cl_2), (*S*)-2-octyloxirane $[\alpha]_D^{24}$ = -8.12 (c = 1.54, CH_2Cl_2)[38]. To further confirm the selectivity ring opening of the epoxide with 2-naphthlene thiol (**3.79**) used by Jacobsen was undertaken.[37] Stirring of the enantiopure epoxide in an ice cold solution of 2-naphthlene thiol, triethylamine and methanol yields the desired (*S*)-1-(naphthalen-2-ylthio) nonan-2-ol (**3.80**) which can be analysed by HPLC. Both chiral and racemic epoxides were successfully ring-opened and analysis confirmed a greater than 98% e.e. of the desired *(S)* product (Scheme 19).



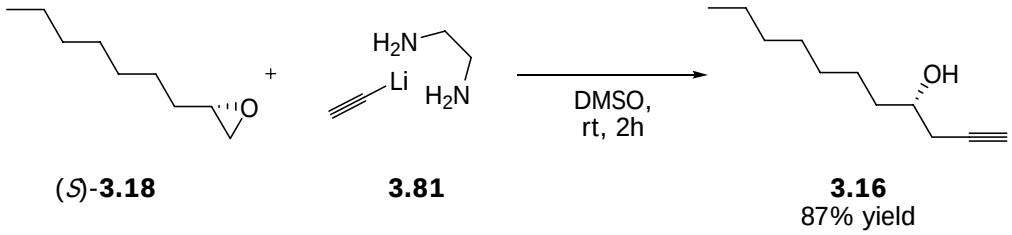
(*S*)-**3.18** **3.79** **3.80**
28% yield
98% e.e.



Scheme 19

The next step was the formation of the homopropargyl alcohol, nucleophilic ring opening of epoxides with alkynes can be achieved with trimethylsilylacetylene and a suitable base. The reaction is not convenient on larger scales due to the large quantities of butyl lithium required. An alternative for epoxides with little functionality is lithium acetylide complexed with ethylene diamine (**3.81**), which is reasonably air stable and has a short reaction time of 2-3 hours. To this end, optically pure (*S*)-2-heptyloxirane (**3.18**) was added to a solution of

lithium-acetylide EDA complex (**3.81**) in anhydrous DMSO. Stirring for 2 hours followed by aqueous work-up led to the desired alcohol (**3.16**) as a golden yellow oil which was of significant purity to continue with the synthesis (Scheme 20).



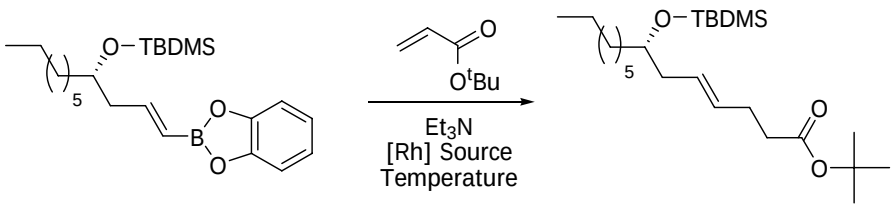
(*S*)-**3.18** **3.81** **3.16**
87% yield

Scheme 20

Two protecting group operations were undertaken for the hydroboration reaction; both the methyl ether (**3.12**) and *tert*-butyldimethylsilyl (TBDMS) (**3.82**) derivatives were prepared by standard procedures. Synthesising the silyl protected ether gave a more protected environment for the oxygen atom and would be more suitable for any hydroboration procedures due to its steric demands. In addition, there was no precedent in the literature for the hydroboration of propargylic methyl ethers. Using a hydroboration agent such a catecholborane with its high affinity for oxygen could lead to elimination of this group from the molecule giving the ene-yne material as previously observed by Li.[19]

3.4 Tandem Hydroboration Conjugate Addition Reactions

Tandem rhodium-catalysed hydroboration-conjugate addition could now be attempted, utilising the procedure outlined by Hayashi.[29] Three alkynes were employed in the initial screening, -OCH_3 and -OTBDMS undec-1-yne derivatives as well as commercially available 1-decyne. The -OTBDMS alkyne was subjected to hydroboration with catecholborane at 70ºC for 3 h generating the alkenyl boronic ester species. The *in-situ* formed material was reacted directly with a rhodium source and unsaturated ester for 16 hours. Although a trace amount of the desired product was observed utilising Hayashi's original conditions with *tert*-butyl acrylate, modifying the conditions gave no significant material for isolation (Table 2).



Entry	[Rh]	Solvent	Temperature	% Conversion[b]
1[a]	$[Rh(acac)(eth)_2]$/ BINAP	Dioxane	80	trace
2	$[Rh(acac)(eth)_2]$/ BINAP	Dioxane	100	trace
3	$[Rh(cod)_2][BF_4]$	Dioxane	100	0
4	$[Rh(cod)Cl]_2$/cod	Dioxane	100	0
5	$[Rh(cod)OH]_2$	Dioxane	25	0

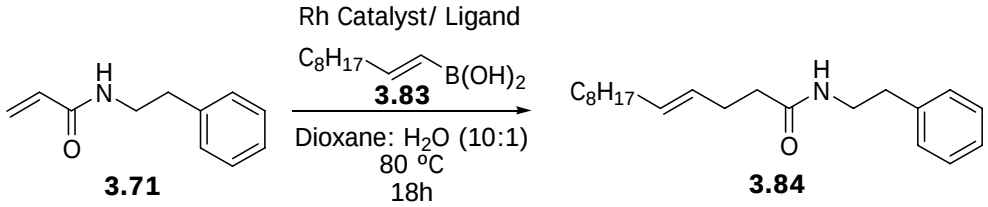
[a] Typical reaction conditions: OTBDMS undec-1-yne, cataceholborane neat (2 eq.), followed by rhodium catalyst (5 mol%), triethylamine (5 eq.), *tert*-butyl acrylate, dioxane/H_2O (10/1), 100°C, 16h.
[b] Conversion by ^1H NMR

Table 2

At this stage it was unknown whether the boron species was forming and the conjugate addition failing. Breaking the reaction down into its component parts and using 1-decyne for simplicity the hydroboration with catecholborane was evaluated. The reaction was heated in a sealed vessel as with previous experiments. After 3 hours the solvent was removed under vacuum and the crude reaction mixture analysed by NMR spectroscopy. Proton NMR showed a mixture of products including starting material, catechol and product in approximately 15% conversion after the suggested time by Hayashi. It was felt that the poor yields of the alkenyl catecholborane species were proving to be the problem and alternative methods of hydroboration should be pursued.

The other step of the synthesis is the rhodium-catalysed conjugate addition to either *tert*-butyl acrylate or *N*-phenylethylacrylamide. Although the unsaturated amide material had not been used in conjugate addition previously, it was deemed a better substrate due to its ease of separation from by-products and its chromophore for TLC analysis. (*E*)-Decenyl boronic acid (**3.83**) was synthesised by the routes of H.C. Brown *et al.*[39] Upon complexing dibromoborane dimethylsulfide complex in dichloromethane with 1-decyne the bright green alkenyl dibromoborane complex was quenched into an ice cold mixture of diethylether and water. Aqueous extraction and subsequent drying gave material of sufficient purity for coupling reactions. It was observed that complete conversion to (*E*)-*N*-phenethyltridec-4-enamide (**3.84**) product from coupling of decenyl boronic acid to *N*-phenylethylacrylamide (**3.71**) was achieved using neutral catalysts and diene ligands such as cod. Gratifyingly the reaction

showed less than 5% of the isomerised product that has been observed in our group when alkenyl boronic acid species are added to substrates without α-substituents. Utilising phosphine ligands hindered the conversion to product with cationic rhodium sources being ineffective in yielding significant amounts of material (Table 3). The other interesting point to note is the general colour change of the catalyst species. Upon addition of a rhodium source, cyclooctadiene, solvent and water to a flask under argon a yellow solution is formed. Subsequent addition of boronic acid gives a red solution with transmetallation of the organometallic to the complex. After addition of substrate in dioxane the red solution persists until reaction is complete and the yellow complex mixture is returned. It was felt at this point a known quantity of organometallic reagent would be preferable to forming the compound *in-situ*.

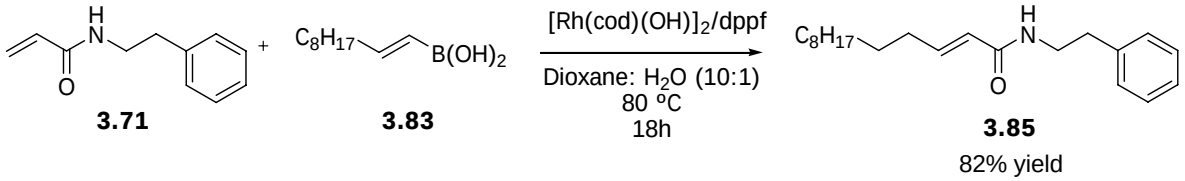


Entry	[Rh]	Ligand	Base	% Yield [b]
1[a]	$[Rh(cod)OH]_2$	cod 10 mol%	-	91
2	$[Rh(cod)OH]_2$	cod 10 mol%	NaOH 20 mol %	87
3	$[Rh(cod)Cl]_2$	cod 10 mol%	-	79
4	$[Rh(cod)OH]_2$	dppb 5.5 mol%	-	55
5	$[Rh(cod)OH]_2$	dppf 5.5 mol%	-	82[c]
6	$Rh(cod)OH]_2$	(*rac*)-BINAP 5.5 mol%	-	38
7	$[Rh(acac)(eth)_2]$	(*rac*)-BINAP 5.5 mol%	-	28
8	$[Rh(cod)_2][BF_4]$	(*rac*)-BINAP 5.5 mol%	-	32
9	$[Rh(nbd)_2][BF_4]$	(*rac*)-BINAP 5.5 mol%	-	35

[a] Typical reaction conditions: N-phenylethyl acrylamide (0.25 mmol), decenyl boronic acid (2 eq.), followed by rhodium catalyst (5 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16h.
[b] Isolated yield after flash chromatography.
[c] Isomerised Material

Table 3

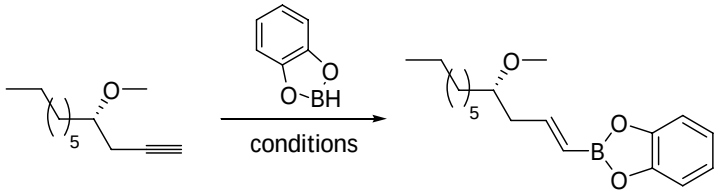
One result of note was the conjugate addition using dppf as the phosphine ligand. Upon work-up a single isomer of (*E*)-N-phenethyltridecenamide was observed although it was not the 4 position as expected. By studying 2D NMR it was determined at the product formed was exclusively the (*E*)-N-phenethyltridec-2-enamide (**3.85**). This was surprising as previous additions of alkenyl boronic acid species in conjugate addition enolate protonation reactions can lead to isomerised products.[40] The "double" isomerisation product is not commonly observed and could be an effect of the bulky electron-rich ligand (Scheme 21).



Scheme 21

3.5 Synthesis of Organoboron Portion of Lyngbic Acid:

In order to form the corresponding organoboronic acid portion of Lyngbic acid a range of routes were studied. Initial studies were based on hydroboration with catecholborane, although this was unsuccessful in the tandem hydroboration-conjugate addition reaction, it was discovered that isolation of the alkenyl boronic acid could be achieved. A range of conditions were screened with no product isolated (Table 4). All NMR traces contained a complex mixture of products with no observed peak in ^{11}B decoupled NMR spectra. A plausible outcome was the formation of the ene-eyne species that has been previously observed with strong bases. Boron reagents are well known for their high affinity for oxygen and the methoxy group could undergo elimination to give the ene-enyne side product. Replacing the methyl protected ether for a more bulky *tert*-butyl dimethylsilyl group gave a similar product outcome.



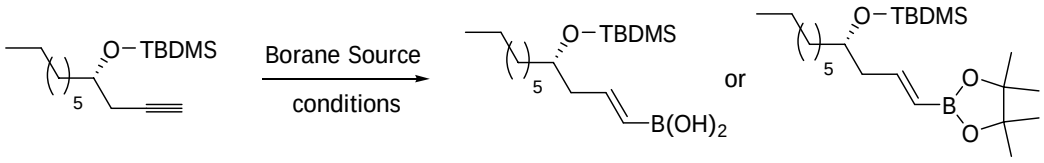
Entry	Catecholborane Source	Temperature	Time	% Conv. [b]
1[a]	Neat	25	48h	0
2	Neat	80	3h	0
3	0.5M in THF	25	72h	0
4	0.5M in THF	70	24h	<5%
5	0.5M in THF	100 microwave	20 minutes	<5%

[a] Typical reaction conditions: terminal alkyne (0.5 mmol), catecholborane source (2 eq.), temp °C.
[b] Conversion by ^{1}H NMR.

Table 4

To this end a range of previously discussed routes to alkenyl boronic acids were attempted. A number of commercially available reagents such as dibromoborane-dimethyl sulfide complex and dichloroborane-dioxane complex were chosen (Table 5).[39, 41, 42] A number of boron-exchange reactions were also attempted with both pinacol and 9-BBN. The exchange of

pinacol with the catecholboronate ether gives a small amount of the desired product for analysis. This was a breakthrough result as pinacolboranes are stable to chromatography and thus could be isolated from any residual by-products. The compound was isolated as a single component after chromatography, and although all attempts to improve yield were unsuccessful, we had demonstrated the chiral propargylic boronate ester could be formed.

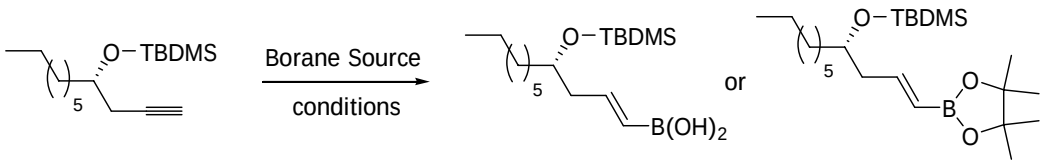


Entry	Borane	Temperature	Time	% Conv. [c]
1[a]	$BHBr_2.SMe_2$	25	3h	0
2[b]	$BHCl_2$. $C_4H_8O_2$	25	16h	0
3	Catecholborane then 9-BBN	70	2h	0
4	Catecholborane then pinacol	70	2h	15 (5%)

[a] Typical reaction conditions: OTBS Alkyne (1.0 mmol), $BHBr_2.SMe_2$ 1M in CH_2Cl_2 (1.05 eq.) 0 ºC, 3h, followed by diethyl ether/H_2O (10/1), 0 °C, 30 minutes.
[b] Typical reaction conditions: OTBS Alkyne (1.0 mmol), $BHCl_2$. $C_4H_8O_2$ 3M in CH_2Cl_2 (1.05 eq.) 25 ºC, 16h, followed by diethyl ether/H_2O (10/1), 0 °C, 30 minutes.
[c] Conversions by ^1H NMR; Yields in parentheses

Table 5

By studying the hydroboration literature, milder routes such as pineneborane hydroboration, followed by formation of the boronic ester with freshly distilled acetylaldehyde, and finally hydrolysis with either water or pinacol should give the desired product.[43] Reactions with borane-THF complex proved unsuccessful with water, due to the instability of the complex. In contrast borane-dimethylsulfide complex gave a low yield of both the pinacol and boronic acid product, although the latter could not be successfully isolated (Table 6). The reaction was time consuming and required fresh distillation of both pinene and acetyladehyde in order to give the yield reported.

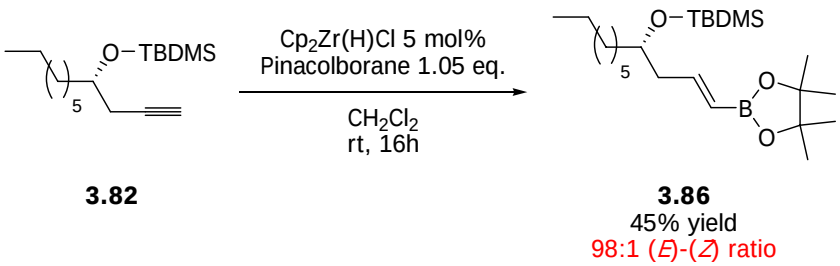


Entry	Borane	Quench	Time	% Conv. [b]
1[a]	BH_3.THF, (α)-Pinene, acetylaldehyde	H_2O	24h	0
2[b]	BH_3.THF, (α)-Pinene, acetylaldehyde	Pinacol	24h	10
3	$BH_3.SMe_2$,(α)-Pinene, acetylaldehyde	H_2O	24h	5
4	$BH_3.SMe_2$, (α)-Pinene, acetylaldehyde	Pinacol	24h	20 (10%)

[a] Typical reaction conditions: Borane Source (1eq.), (α)-Pinene (1.05 eq.), rt 3h followed by OTBS Alkyne (1.0 mmol), 2h 25 ºC, 16h, followed by acetylaldehyde reflux (16h). H_2O 25 °C, 30 minutes.
[b] As [a] quenching with pinacol in anhydrous THF (5 mL)
[c] Conversions by ^{1}H NMR; Yields in parentheses

Table 6

At this juncture it was decided that a direct boronation would not give yields suitable for further transformations. A route of trapping an organometallic species with pinacolborane or metal-catalysed hydroboration was considered. Knochel has shown previously that pinacolborane can be used as an improved hydroboration reagent, which gave air and moisture stable boronic esters with yields and selectivity being vastly improved from using catchecolborane.[44] Combining this reagent with organozirconium reagents is a promising alternative to pre-existing hydroboration methodology allowing sensitive functionality to be incorporated successfully. The organozirconium species can be formed *in-situ* by reaction of a terminal alkyne with Schwartz Reagent, giving the corresponding alkenylzirconium species.[45, 46] Early reports of the reaction were undertaken by Srebnik and co-workers with a solution of alkyne, pinacolborane and Schwartz reagent in a solution of dry dichloromethane giving the desired product in high yields.[47, 48] The reaction has some advantages; reaction occurs at low temperature and side-products that arise from catecholborane based systems are minimised. Using the TBDMS protected ether derivative (**3.82**), and pinacolborane (1.05 eq.) under analogous conditions to Srebnik gave a 45% yield of the desired (*E*)-alkenyl boronic ester (**3.86**) (*Scheme 22*). Upon increasing the quantities of Schwartz reagent (10 mol%) and pinacolborane (1.5 eq.) gave only a small improvement in yield (48%). Comparisons with no Schwartz reagent present gave a conversion of 10% by ^{1}H NMR analysis.



Scheme 22

Wang and co-workers have presented an improved process for the preparation of (*E*)-vinylboronate esters using Schwartz reagent (**3.87**).[49] They determined that with an allylic or propargylic ether (**3.88**) an undesired Zr-O bond could form (**3.89**) leading to difficulty in reforming the catalyst and leading to the undesired (*Z*)-isomer (**3.90**) (*Figure 6*). This could be rectified by heating the reaction mixture to 60 ºC, and adding an amine base such as DMAP or triethylamine, to remove this interaction giving the (*E*)-zirconiate species (**3.91**). Trapping this compound with pinacolborane (**3.92**) provides optimum yields and excellent selectivity of the (*E*)-pinacolboronate isomer (**3.93**).

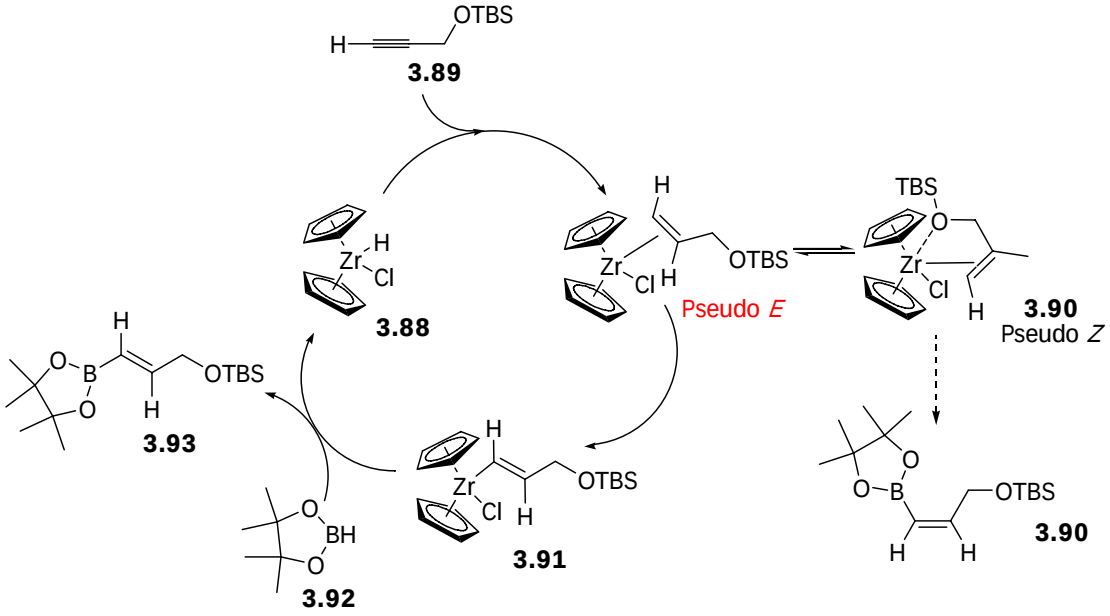
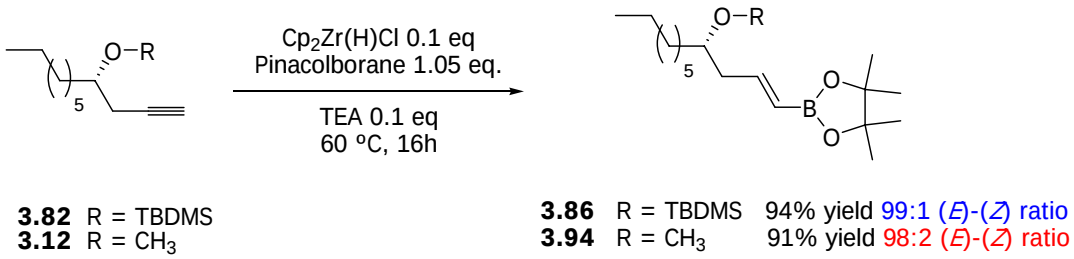


Figure 6

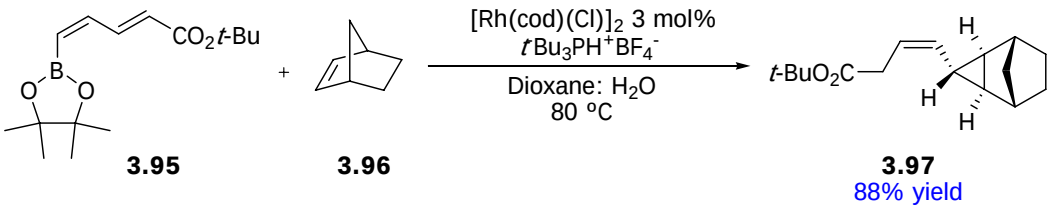
This methodology was used on the TBDMS protected terminal alkyne derivative (**3.82**) with 0.1 equivalents of Schwartz reagent and 0.1 equivalents of anhydrous triethylamine. The reaction was carried out in neat pinacolborane as the solvent heating to 60 ºC overnight, with no exposure to light due to the sensitivity of the Schwartz reagent to decomposition (*Scheme*

23). The reaction occurred with complete conversion to the alkenyl pinacol boronic ester (**3.86**) and purification could be rapidly achieved *via* stirring with hexane to precipitate excess pinacol and filtering through a short silica column eluting with hexanes. Subjecting the methyl ether derivative (**3.12**) which had caused problems with this transformation previously, worked equally well giving a 91% yield (**3.94**); thus removing a protection group operation from the total synthesis. By this route the reaction was reproducible with 5 g of product synthesised in a rapid manner in one pot with under neat conditions.



Scheme 23

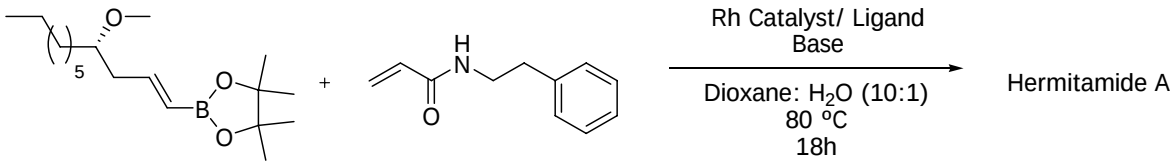
With the desired protected organoboronic ether species available, rhodium-catalysed conjugate additions could now be effectively screened. There are only a handful of reactions in which pinacolboronate reagents are used successfully in conjunction with rhodium-catalysed conjugate addition.[50-54] For the purpose of our studies the work published by Lautens and co-workers with rhodium-catalysed addition of vinyl boronate esters (**3.95**) with unactivated alkenes (**3.96**) showed promise for cyclopropanation products (**3.97**) (*Scheme 24*).[53]



Scheme 24

Using phenylethylacrylamide with the methyl ether pinacolboronic ester derivative and $[Rh(cod)Cl]_2$ as the rhodium source in a dioxane water mixture gave no conversion to the desired Hermitamide A structure (Table 7). Changing the rhodium source to the preformed more active $[Rh(cod)(OH)]_2$ catalyst gave no improvements, yielding only the starting material and unreacted pinacolboronate. The addition of a range of bases such as Na_2CO_3, LiOH and NaF and organic base triethylamine in order to form the more reactive boronate species also gave no improvement in the reaction. A final attempt at boronate formation was

by the route of Kobayashi where the boronate species is stirred in the presence of methyl lithium for 15 minutes at 0 ºC prior to reaction.[55] This route gave a trace of product formation, although the predominant species by NMR were still the pinacolboronic ester and acrylamide. In addition to this the NMR showed possible contamination of an unknown by-product.



Entry	[Rh]	Ligand	Base	% Conversion [c]
1 [a]	$[Rh(acac)(eth)_2]$	cod 10 mol%	-	0
2	$[Rh(cod)_2][BF_4]$	-	-	0
3	$[Rh(nbd)_2][BF_4]$	-	-	0
4	$[Rh(cod)Cl]_2$	-	-	0
5	$[Rh(cod)Cl]_2$	cod 10 mol%	Na_2CO_3 1 eq	0
6	$[Rh(cod)Cl]_2$	cod 10 mol%	NaOH 1 eq	0
7	$[Rh(cod)Cl]_2$	cod 10 mol%	LiOH 20 1 eq	0
8	$[Rh(cod)Cl]_2$	cod 10 mol%	NaF 1 eq	0
9	$[Rh(cod)Cl]_2$	cod 10 mol%	TEA	0
10	$[Rh(cod)OH]_2$	cod 10 mol%	Na_2CO_3 1 eq	0
11 [b]	$Rh(cod)OH]_2$	cod 10 mol%	MeLi	5%

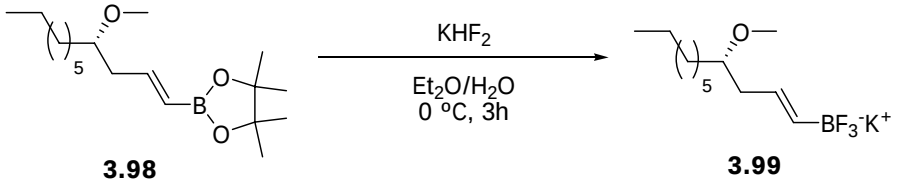
[a] Typical reaction conditions: N-phenylethyl acrylamide (0.25 mmol), (*S,E*)-2-(4-methoxyundec-1-enyl)-pinacol ester (2 eq.), followed by rhodium catalyst (5 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16h.
[b] As [a] but with MeLi (2 eq.) added to boronic ester at 0 ºC prior to reaction.
[c] Conversion by ^1H NMR spectroscopy

Table 7

It was clear that either the free boronic acid species would have to be formed or a more reactive and stable boronate species would need to be isolated. Removal of the diol protecting group in boronic esters is difficult with only few methods published.[56, 57] Methods currently available for the deprotection of pinacolyl esters generally include destructive procedures such as use of periodate to cleave the protecting diol oxidatively as well as hydrolytic protocols.[56] Transesterification using polystyrene boronic acids can also be carried out with reasonable success.[57] In general all deprotection reactions suffer from incomplete conversions or problems in separating the desired boronic acid from a large excess of transesterification partner.

In contrast there is a large amount of literature precedent in the conversion of pinacolboronic esters to the corresponding potassium trifluoroborate salts.[58-60] Subjecting the Lyngbic acid

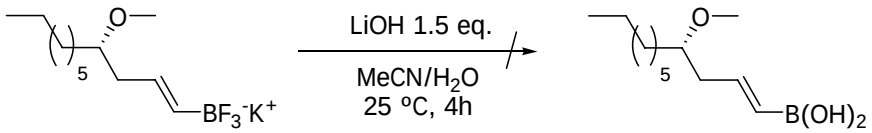
precursor boronate ester (**3.94**) to modified conditions proposed by Genet and Vedejs,[59, 61] using diethyl ether as the solvent and cooling to 0 ºC with stirring for 3 hours led to a low yield of 44% (*Scheme 25*). The reaction was not very reproducible with yields varying dramatically, respectable quantities of organotrifluoroborate salt (**3.99**) were observed when solvent was removed with minimal heating (~30 ºC), the precipitated salts were washed successively with chilled or room temperature acetone, rather than hot solvent as previously described.[61] Upon chilling in a freezer for 3 days up to 2 g of product could be collected and stored indefinitely in the presence of air and water. NMR studies showed a single component by multinuclear analysis and no pinacol was observed after trituration. The highly crystalline solid was also deemed to be >99% e.e. after a single recrystallisation from acetone-diethyl ether.



3.98 **3.99**

Scheme 25

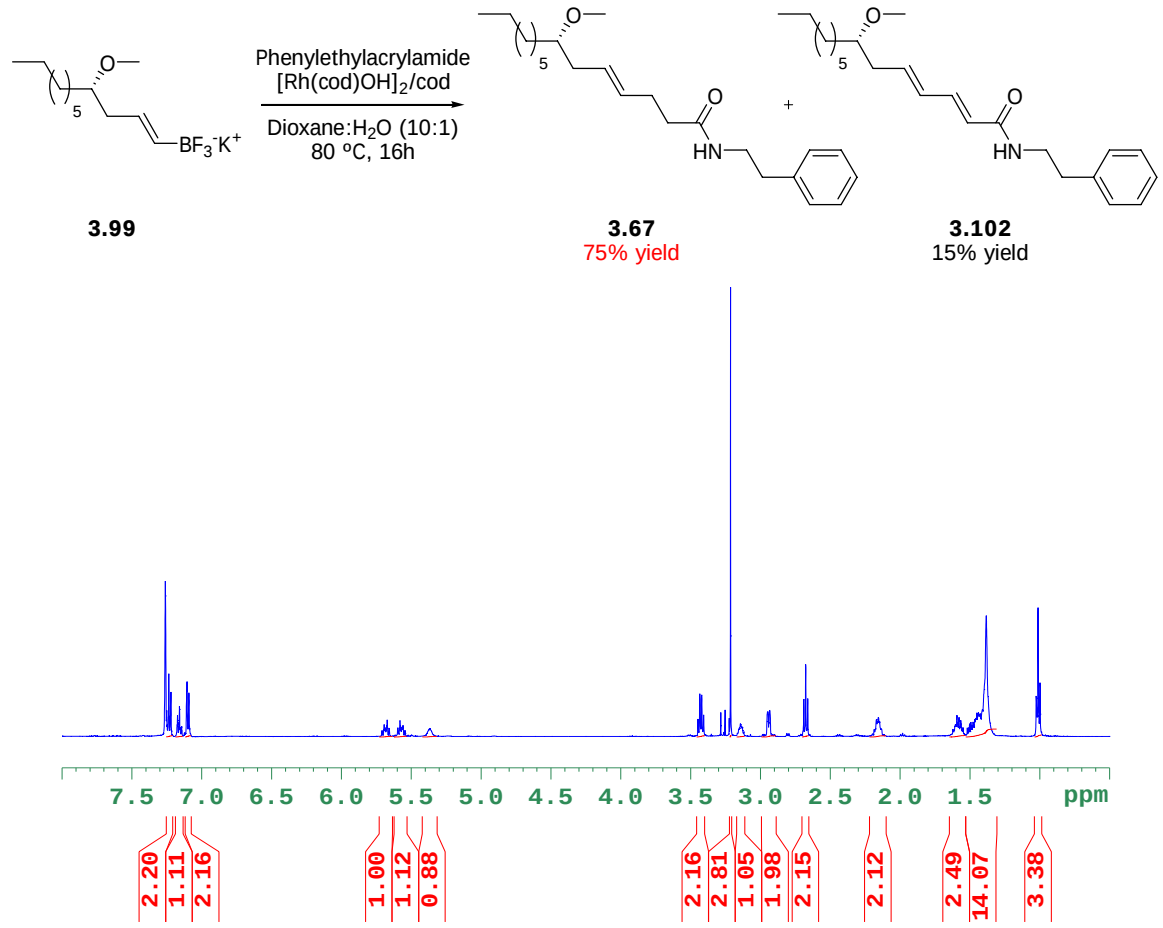
For completeness the procedure of Yuen was followed to convert a small quantity of the newly formed potassium trifluoroborate salt (**3.99**) into the corresponding alkenyl boronic acid material (**3.100**).[62] The method uses a solution of lithium hydroxide in acetonitrile to convert the potassium salt in quantitative yield for a range of substituted aryl potassium trifluoroborates. Using these conditions the Lyngbic acid potassium trifluoroborate precursor was deprotected to boronic acid, upon work-up a white gum was isolated which had significant decomposition materials, such as boronic anhydride formation (*Scheme 26*). The compound could not be successfully purified from the impurities and upon standing in air overnight the compound blackened and was unsuitable for further transformations.



3.99 **3.100**
decomposes

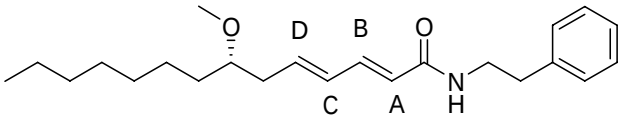
Scheme 26

Synthesis of the potassium trifluoroborate coupling reagent allowed the synthesis of the final product. Reactions of phenylethylacrylamide with 2 equivalents of potassium trifluoroborate salt (**3.99**) in the presence of [Rh(cod)$(OH)_2$] and 10 mol% cyclooctadiene as the ligand lead to an active catalyst system. By this route complete conversion to product was observed with no starting material remaining. However, two spots were observed with similar R_F values suggesting two separate products. Careful column chromatography gave both the desired Hermitamide A natural product (**3.67**) as well as a diene side-product (**3.101**) in a 5:1 ratio (*Scheme 27)*.

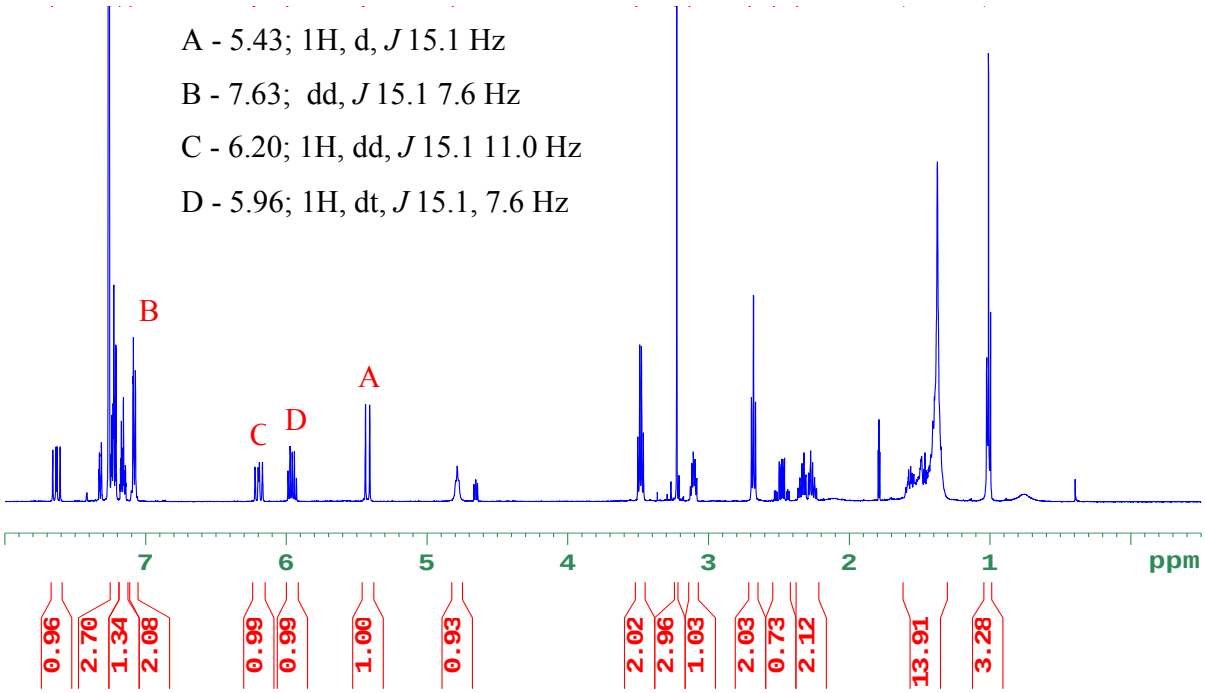


Scheme 27

The two compounds could be unambiguously assigned by ^{1}H NMR spectroscopy based on literature values of authentic Hermitamide A.[63] The key signals to note in the beta-hydride elimination side-product were the alkenyl protons A, B, C, D which can be readily assigned by ^{1}H NMR and 2D correlation experiments. By studying the coupling constants in the reaction the signals are clearly the Heck-type product, this was supplemented with accurate mass spectrometry showing the desired molecular ion (Scheme 28).



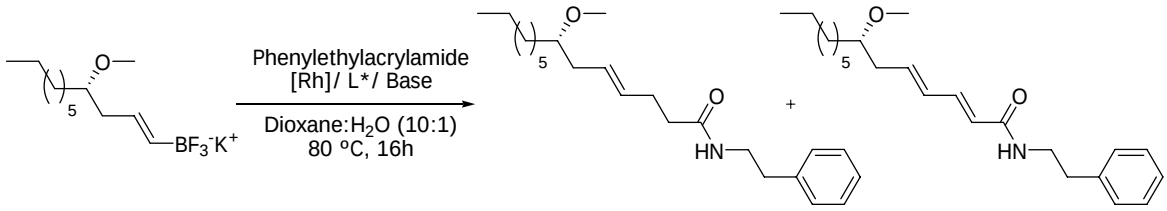
3.101



Scheme 28

Studying other catalyst-ligand systems it was hoped to improve this ratio or to preferentially form one of the two products. Using other neutral catalysts such as $[Rh(acac)(C_2H_4)_2]$ and $[Rh(nbd)Cl]_2$ gave no improvement in selectivity (Table 8). Other rhodium complexes using achiral bidentate phosphine ligands such as dppb, and dppf lead to a lower conversion to product, suggesting that diene ligands give improved turnover of reaction over phosphine based systems. The only effective method of suppressing formation of the diene product was by using greater than 4 equivalents of trifluoroborate salt. This was not the ideal solution to the reaction as using the chiral material in four-fold excess was not atom-efficient as a process, especially as the acrylamide portion was inexpensive and readily available. To this end reaction were continued with 2 equivalents of the chiral material to give the best compromise. Reactions could be achieved with 1.5 eq. of trifluoroborate salt although the ratio of products was poor (60: 40 conjugate addition-Heck type). Upon purification the product was isolated as a colourless oil as outlined in the literature, NMR analysis and mass spectrometry confirmed

the correct structure of Hermitamide A, and optical rotations in chloroform as used in the literature gave similar values - $[\alpha]_D^{20}$ = -9.1 º (*c*=1.05, $CHCl_3$); lit = -9.3 º (c=1.2, $CHCl_3$).[63] This suggested that no scrambling of the methoxy chiral centre had occurred during salt formation and subsequent coupling reactions.

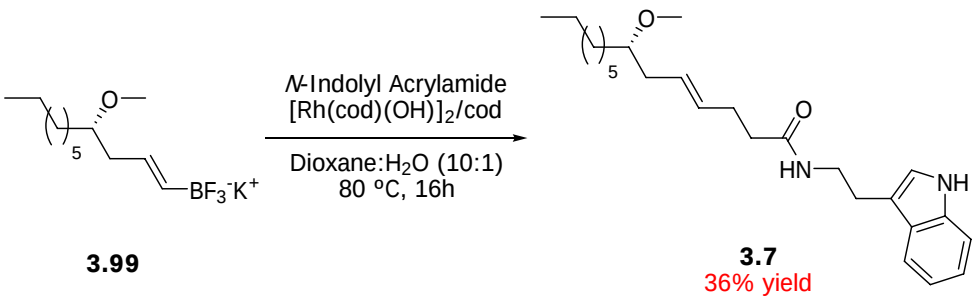


Entry	[Rh]	Ligand	Base	% Conv A [b, c]
1 [a]	$[Rh(acac)(eth)_2]$	cod 10 mol%	-	12
2	$[Rh(cod)_2][BF_4]$	-	-	62 (14%)
3	$[Rh(nbd)Cl]_2$	-	-	0
4	$[Rh(nbd)_2][BF_4]$	-	-	22
5	$[Rh(cod)OH]_2$	cod 10 mol%	-	83 (72%)
6	$Rh(cod)OH]_2$	dppb 5 mol%	-	40
7	$Rh(cod)OH]_2$	dppf 5 mol%	-	37
8	$Rh(cod)OH]_2$	cod 10 mol%	NaF 1 eq	53 (12%)
9	$Rh(cod)OH]_2$	cod 10 mol%	LiOH 1 eq.	15
10[d]	$Rh(cod)OH]_2$	cod 10 mol%	-	91 (81%)

[a] Typical reaction conditions: N-phenylethyl acrylamide (0.25 mmol), (*S,E*)-2-(4-methoxyundec-1-enyl)-trifluoroborate (2 eq.), followed by rhodium catalyst (2 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16h.
[b] Conversion by ^1H NMR spectroscopy
[c] Yields in parentheses.
[d] Using 4 equivalents of BF_3K salt

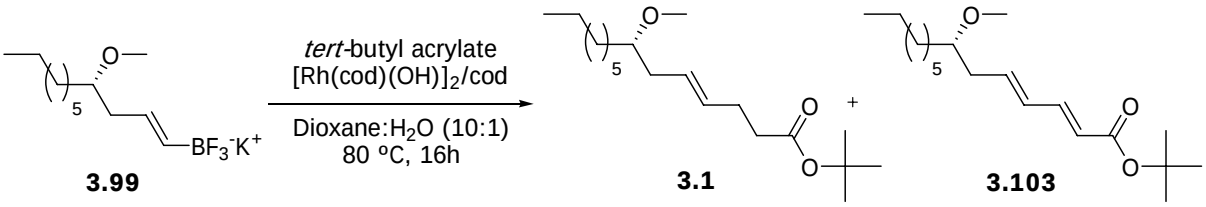
Table 8

Attempts were then turned to the synthesis of Hermitamide B (**3.7**); this was seen as a challenging compound due to the inactivity of the tryptamine acrylamide derivative. Using the conditions for synthesis of Hermitamide A; 2 mol% rhodium catalyst, 10 mol% cod, dioxane:water 10:1 gave a low conversion to product with a number of side-products based on isomerisation of the alkene bond, these impurities could not be successfully removed from product by column chromatography. Upon changing the conditions to use a higher catalyst loading – 5 mol% rhodium and 4 equivalents of potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate a significant amount of product could be isolated successfully. Comparisons of analytical data in conjunction with optical rotations showed the final synthesis of optically pure Hermitamide B was achieved in a single reaction vessel (*Scheme 29*).



Scheme 29

Finally the formation of Lyngbic acid (**3.1**) was attempted for completeness of the methodology. Conjugate-addition of potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate (**3.99**) to a commercially available acrylate ester such as *tert*-butyl acrylate with subsequent deprotection should provide a large scale route to enantiopure Lyngbic acid. Upon subjecting *tert*-butyl acrylate to our standard conditions it was found that a mixture of Lyngbic acid (**3.1**) and diene side-product (**3.103**) was formed in a 1:1 ratio of products by ^{1}H NMR analysis which could not be separated by column chromatography. This ratio could not be improved by adding extra organoboron reagent, so addition of an organic or inorganic base was attempted (Table 9). Using bases such as triethylamine and sodium fluoride led to improved formation of the conjugate-addition product, however, the optimum results occurred with barium hydroxide as a base giving a single product after column chromatography.

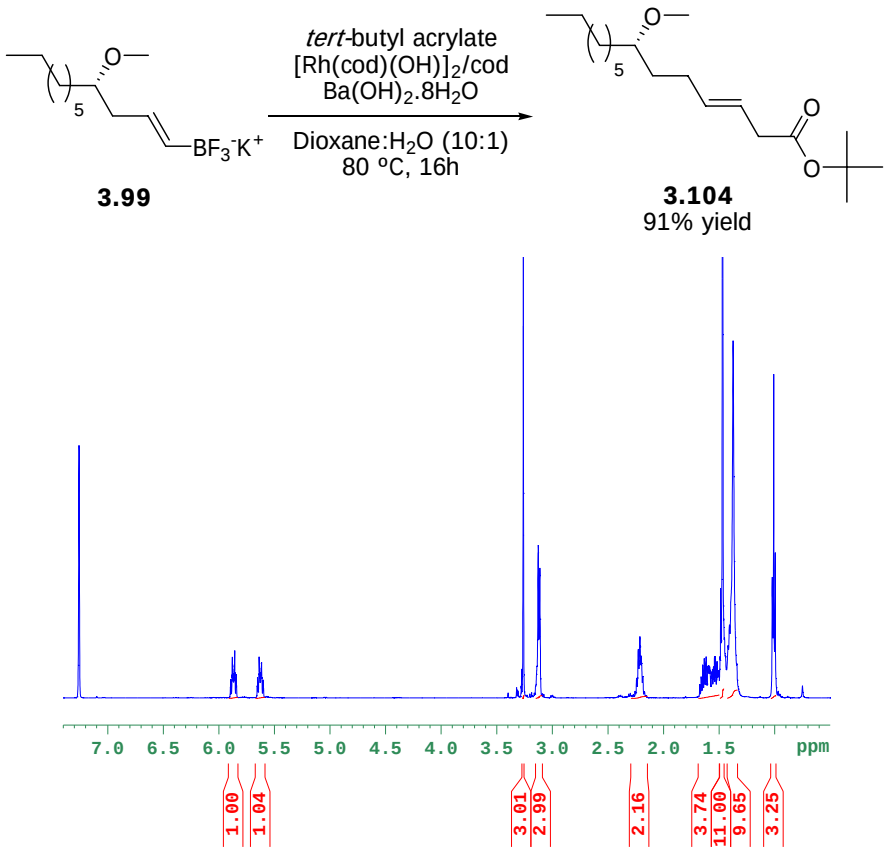


Entry	Base	% Conv A [b]	% Yield [c]
1 [a]	-	45	55
2	Et_3N	52	48
3	NaF	60	40
4	CsF	63	37
5	$Ba(OH)_2.8H_2O$	100 (95%)	91

[a] Typical reaction conditions: *tert*-butyl acrylate (0.25 mmol), decenyl pinacolboronate (2 eq.), base 1 eq.), followed by rhodium catalyst (2 mol%), ligand, dioxane/H_2O (10/1), 80 °C, 16h.
[b] Conversion by ^{1}H NMR
[c] Isolated yield

Table 9

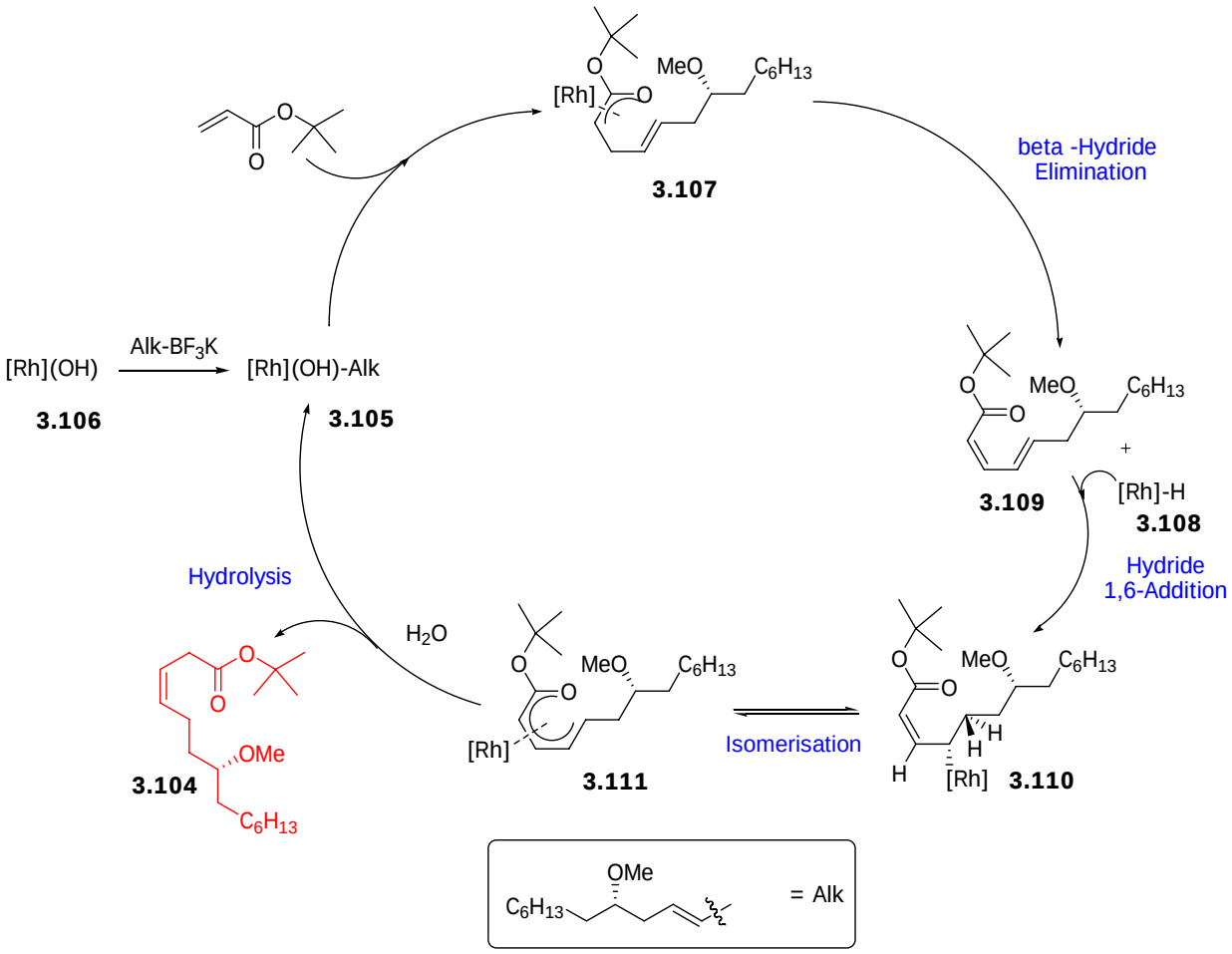
Upon analysis of the product by NMR spectroscopy it was found that the isolated product was not Lyngbic acid by comparison of known literature data. The 1-proton quintet observed for C-8 was not observed, and instead a 2-proton multiplet was overlapping the signal, in addition to this a new resonance at 2.20 ppm correlating to only the alkene protons was observed by ^{1}H COSY experiments. The geometry of the alkene was observed to be the (*E*)-isomer showing complete transfer of olefin geometry from the organotrifluoroborate species. On this basis it was deduced that the observed product was the isomerised (*S,E*)-*tert*-butyl 7-methoxytetradec-3-enoate (**104**) and not Lyngbic acid as expected (*Scheme 30*).



Scheme 30

The mechanistic rational for the bond isomerisation is possibly due to 1,6-addition of a rhodium-hydride species. Although such conjugate 1,6-additions are rare, a number of examples have been reported, especially with highly reactive organometallic species such as organozinc[64, 65] and more recently Grignard reagents.[66] The proposed catalytic cycle proceeds through the active rhodium-alkenyl species (**3.105**) formed from the corresponding rhodium-hydroxy complex (**3.106**) with alkenyl trifluoroborate salt (*Scheme 31*). Subsequent insertion of the alkenyl fragment into *tert*-butyl acrylate generates the rhodium-oxa-π-allyl

intermediate (**3.107**), leading to two possible regeneration pathways – hydrolysis regenerating the active rhodium-hydroxy catalyst, or β-hydride elimination yielding a rhodium-hydride intermediate (**3.108**). Rhodium hydride species are well known but are believed to be intolerant to moisture. Contrary to this Herrmann *et al* have shown that rhodium-hydride species exist in equilibrium with rhodium-hydroxy species in aqueous systems.[67] To this end a β-hydride elimination pathway leads to the dienoate species (**3.109**) which in turn can react in a 1,6-conjugate addition fashion with the newly formed hydride complex giving hydride addition to the dienoate (**3.110**). The η-1 alkyl rhodium complex is less stable and this leads to isomerisation to a oxa-π-pentadienyl-Rh(I) complex (**3.111**). The oxa-π-pentadienyl-Rh(I) complex can then give rise to the final 1,6-conjugate addition products either by α-protonation or *syn-β*-hydride elimination. In the presence of an inorganic base such as barium hydroxide, hydrolysis of the rhodium-enolate leads to the isomerised material as the sole product (**3.104**), along with regenerating the active rhodium-catalyst.



Scheme 31

The rationale for the increased ability of amide species to give conjugate addition as the major product is a more complex problem. Using enolisation tendencies fails due to esters and amides exhibiting similar properties. It is postulated that the coordination of nitrogen from the amide into the η^1-alkyl rhodium species leads to greater stability than the corresponding oxygen species. Such *N*-Rh chelation will lead to the less of the oxa-π-allyl rhodium species being observed in the catalytic cycle suppressing the competing β-hydride elimination pathway, thus increasing tendency towards a hydrolysis route giving the desired product. The ester product will be made less stable by the *tert*-butyl ester group due to steric demands minimising the Rh-O chelation further, explaining the 1:1 mixture of conjugate-addition to β-hydride elimination products (*Figure 7*).

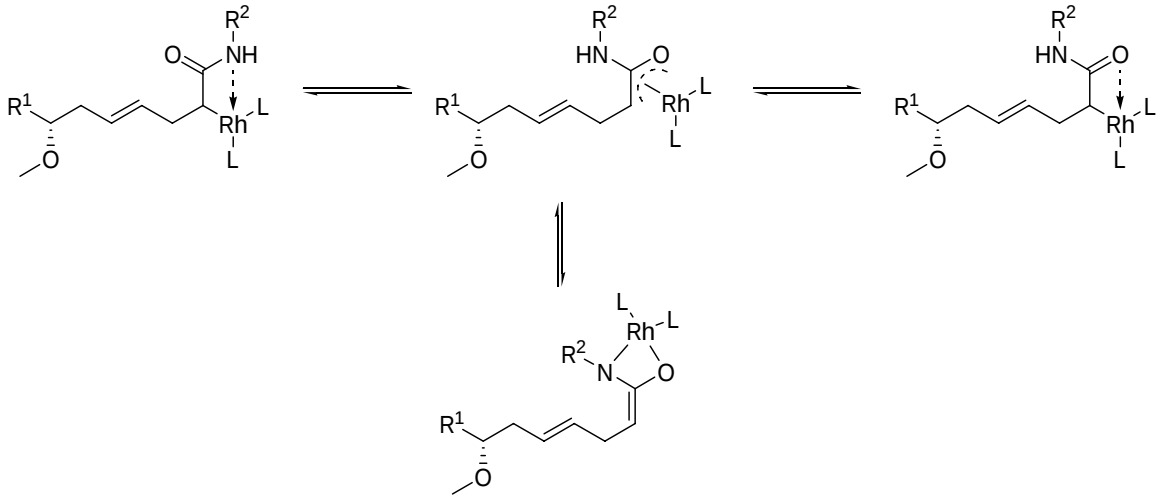
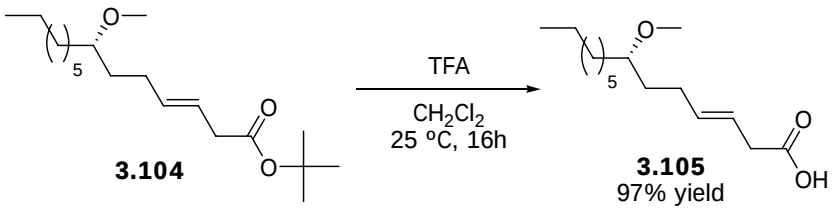


Figure 7

The final step in the synthesis is the deprotection of the *tert*-butyl ester to give the *iso*-Lyngbic acid structure (*S,E*)-7-methoxytetradec-3-enoic acid (**3.105**). Stirring of the reaction materials in a mixture of dichloromethane and trifluoroacetic acid gives the desired product in quantitative yield after column chromatography. The product displays similar properties to Lyngbic acid and shows that deprotection could be readily achieved if Lyngbic acid could be successfully isolated (*Scheme 32*).



Scheme 32

3.6 Conclusion

A novel approach to the Hermitamide natural product family has been successfully developed using a novel chiral potassium trifluoroborate to introduce the fatty acid side chain and chiral information in a single step. By using novel coupling materials in the reaction to previously studied acrylates a novel hydride addition step has been initially observed, further work is required to elucidate a possible mechanism and control the position and geometry of the newly formed alkene products.

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Chapter 4 Experimental

4.1 General Information

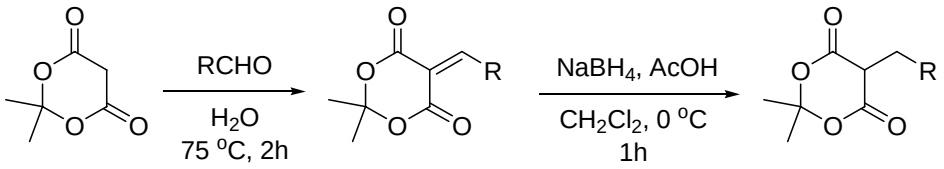
All air-sensitive reactions were carried out under dry nitrogen or argon atmospheres using standard Schlenk line techniques.[1] Dichloromethane and tetrahydrofuran were dried and degassed under an argon atmosphere over activated alumina columns using an Innovative Technology Solvent Purification System (SPS) and degassed using argon prior to use in air sensitive reactions. All secondary and tertiary amines were purified by distillation using calcium hydride as a drying agent and stored under argon in Young's ampoules over 4 Å molecular sieves.

NMR spectra were recorded on Bruker AV300 or AVANCE 400 spectrometers at 298 K unless otherwise stated. ^{1}H NMR spectra were referenced internally to residual protio-solvent ($C\mathit{H}Cl_3$ at 7.26 ppm), ^{13}C NMR spectra referenced to deuterio-solvent resonance ($\mathit{C}DCl_3$ at 77.0 ppm) and ^{31}P NMR spectra were referenced to 85% $H_3\mathit{P}O_4$ (0.00 ppm). Assignments were supported by ^{13}C PENDANT NMR and homo- and hetero-nuclear, one- and two-dimensional experiments as appropriate. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). Coupling constants (*J*) are expressed in Hertz (Hz). The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however the characteristic features of an AA'BB' system were observed in the NMR spectra.

High Performance Liquid Chromatography (HPLC) was performed on Perkin Elmer IBN series system, which uses chiral columns such as Chiralpak OD-H by Daicel Chemical Industries Ltd.

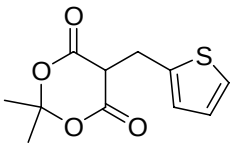
IR spectra were recorded on a Nicolet – Nexus FTIR spectrometer, over the range 4000 – 200 cm^{-1} and averaged over 32 scans, using KBr discs or NaCl plates. Elemental analyses were carried out at the University of Bath using an Exeter Analytical CE 440 elemental analyser.

4.1.2 Conjugate Reduction of Benzylidine Meldrum's acid derivatives to the corresponding 5-monobenzyl species.



2,2-Dimethyl-[1,3]dioxane-4,6-dione (6.43 g, 46.0 mmol) was added portion-wise to a stirred suspension of aryl carboxaldehyde (5.00 g, 44.6 mmol) in water (65 mL) at 23 ºC. A reflux condenser was attached and the mixture stirred at 75 ºC for 2 hours. After cooling to room temperature, the precipitated solid was collected by Buchner filtration, and washed successively with ice-cold water (2x 100 mL), pentane (100 mL) then dried thoroughly. The crude arylidene (1.50 g, 6.30 mmol) was subsequently dissolved in CH_2Cl_2 (100 ml) and cooled to 0 ºC (Ice/NaCl). Acetic acid (5 mL) was added with stirring for 5 minutes under N_2. Sodium borohydride (0.710 g, 26.84 mmol) was then added portion-wise over 1 hour or until the solution turned colourless. The reaction was quenched with water (50 ml) and extracted with CH_2Cl_2 (50 ml). The combined organic extracts were washed with brine (2 x 75 ml) and water (2 x 75 ml) and dried ($MgSO_4$), yielding the title compound which could be used without further purification. For analytically pure compound recrystalisation was undertaken using hot ethyl acetate and hexanes.

4.1.2.1: 2,2-Dimethyl-5-thiophen-2-ylmethyl-[1,3]-dioxane-4,6-dione (2.66)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2-thiophene carboxaldehyde (1.11 g, 10.0 mmol) followed by sodium borohydride (0.710 g, 26.8 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.47 g, 98% yield);

mp (EtOAc) 128 °C;

ν_{max} (KBr)/cm^{-1} 3100, 3014, 2936 (C-H); 1778, 1744 (C=O); 1298 (C-S);

δ_H (300 MHz; $CDCl_3$); 8.03 (1H, dd, *J* 5.0, 1.3 Hz, C*H* Ar); 7.10-7.02 (1H, m, C*H* Ar); 6.94-6.90 (1H, m, C*H* Ar); 3.76 (1H, t, *J* 4.6 Hz, C*H*); 3.72 (2H, d, *J* 4.6 Hz, CH_2); 1.76 (3H, s, CCH_3); 1.59 (3H, s, CCH_3);

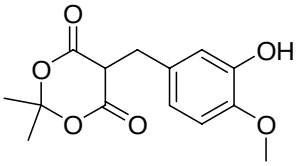
δ_C (75.5 MHz; $CDCl_3$) 164. 9, 138.1, 127.9, 126.8, 125.0, 105.3, 48.2, 28.3, 27.1, 26.4.

MS (EI/CI) *m/z*; 258 ($M+NH_4^+$); 240 (5%, MH^+); 173 (50% $C_8H_{10}OS+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{11}H_{16}O_4N_1S_1$ [$M+NH_4^+$]: *m/z* 258.0795 found: *m/z* 258.0791

Anal. *calcd* for $C_{11}H_{12}O_4S_1$; C, 55.0; H, 5.03; Found: C, 54.2; H, 4.96.

4.1.2.2: 5-(3-hydroxy-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.71)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), vanillin (1.52 g, 10.0 mmol) followed by sodium borohydride (0.721 g, 27.0 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.00 g, 66% yield);

mp (EtOAc) 133 °C;

ν_{max} (KBr)/cm^{-1} 3400 (O-H); 2831 (C-O-CH_3); 1778, 1754 (C=O).

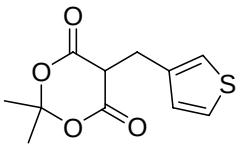
δ_H (300 MHz; $CDCl_3$); 6.85 (1H, br s, C*H* Ar); 6.81-6.79 (2H, m, C*H* Ar); 5.56 (1H, s, O*H*); 3.82 (3H, s, OCH_3); 3.72 (1H, t, *J* 4.9 Hz, C*H*); 3.42 (2H, d, *J* 4.9 Hz, CH_2); 1.72 (3H, s, CCH_3); 1.47 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 166.0, 146.7, 145.2, 129.3, 123.0, 114.8, 113.1, 105.7, 56.3, 48.8, 32.40, 28.9, 27.8.

HRMS (ESI^+) *calcd* for $C_{14}H_{16}Na_1O_6$ [M+Na^+]: *m/z* 303.0845 found: *m/z* 303.0822

Anal. *calcd* for $C_{14}H_{16}O_6$; C, 60.0; H, 5.75. Found: C, 60.8; H, 5.81.

4.1.2.3: 2,2-Dimethyl-5-thiophen-3-ylmethyl-[1,3]-dioxane-4,6-dione (2.72)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 3-thiophene carboxaldehyde (1.11 g, 10.0 mmol), followed by sodium borohydride (0.710 g, 26.8 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.38 g, 91% yield);

mp (EtOAc) 81-83 °C;

ν_{max} (KBr)/cm^{-1} 3102, 3014, 2936 (C-H); 1774, 1744 (C=O); 1298 (C-S);

δ_H (300 MHz; $CDCl_3$); 7.22 (1H, dd, *J* 4.9, 3.0 Hz, C*H* Ar); 7.18-7.72 (1H, m, C*H* Ar); 7.02 (1H, dd, *J* 4.90, 1.13 Hz, C*H* Ar); 3.74 (1H, t, *J* 4.6 Hz, C*H*); 3.50 (2H, d, *J* 4.6 Hz, CH_2); 1.73 (3H, s, CCH_3); 1.51 (3H, s, CCH_3);

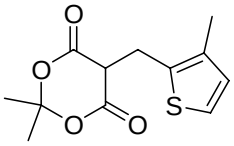
δ_C (75.5 MHz; $CDCl_3$); 165.0, 135.6, 132.3, 129.8, 123.0, 105.2, 48.9, 28.3, 27.0, 24.5, 13.8.

MS (EI/CI) *m/z*; 258 (M+NH_4^+); 240 (5%, MH^+); 173 (45% $C_8H_{10}OS$+NH_4^+);

HRMS (CI^+) *calcd* for $C_{11}H_{16}O_4N_1S_1$ [M+NH_4^+]: *m/z* 258.0795 found: *m/z* 258.0789

Anal. *calcd* for $C_{11}H_{12}O_4S_1$; C, 55.0; H, 5.03; Found: C, 54.4; H, 4.98.

4.1.2.4: 2,2-Dimethyl-5-(3-methyl-thiophen-2-ylmethyl)-[1,3]-dioxane-4,6-dione (2.73)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 3-methyl 2-thiophene carboxaldehyde (1.26 g, 10.0 mmol), followed by sodium borohydride (0.710 g, 26.8 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.33 g, 83% yield);

mp (EtOAc) 78-80 °C;

ν_{max} (KBr)/cm^{-1} 3108, 3007, 2987 (C-H); 1785, 1741 (C=O); 1298 (C-S);

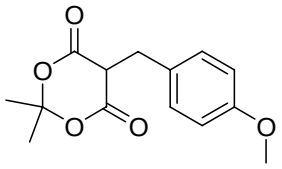
δ_H (300 MHz; $CDCl_3$), 6.98 (1H, d, *J* 4.9 Hz, Ar); 6.64 (1H, d, *J* 4.9 Hz, Ar); 3.78 (1H, t, *J* 4.6 Hz, C*H*); 3.53 (2H, d, *J* 4.6 Hz, CH_2); 2.18 (3H, s, CH_3); 1.69 (3H, s, CCH_3); 1.54 (3H, s, CCH_3)

δ_C (75.5 MHz; $CDCl_3$) 165.0, 135.6, 132.3, 129.8, 123.0, 105.2, 47.9, 28.3, 26.9, 24.5, 13.8.

HRMS (CI^+) *calcd* for $C_{12}H_{18}O_4N_1S_1$ [$M+NH_4^+$]: *m/z* 272.0957 found: *m/z* 272.0924

Anal. *calcd* for $C_{12}H_{14}O_4S_1$; C, 56.7; H, 5.55; Found: C, 56.2; H, 5.49.

4.1.2.5: 5-(4-Methoxy-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.74)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 4-methoxybenzaldehyde (1.36 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 26.8 mmol), were reacted under the standard protocol to generate the desired compound as a white solid (1.49 g, 98% yield).

mp (EtOAc) 82-85 °C (lit = 85-86 °C)[2];

ν_{max} (KBr)/cm^{-1} 3006, 2961, 2915 (C-H); 1787, 1746 (C=O);

δ_H (300 MHz; $CDCl_3$); 7.24 (2H, d, *J* 8.7 Hz, C*H* Ar); 6.81 (2H, d, *J* 8.7 Hz, C*H* Ar); 3.77 (3H, s, OCH_3); 3.72 (1H, t, *J* 4.9 Hz, C*H*); 3.44 (2H, d, *J* 4.9 Hz, CH_2); 1.72 (3H, s, CCH_3); 1.48 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 165.3, 158.6, 130.8, 129.0, 113.8, 105.1, 55.1, 48.1, 31.3, 28.3, 27.1.

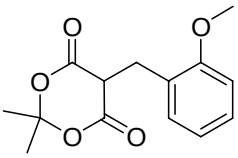
(EI/CI) *m/z*; 258 ($M+NH_4^+$); 240 (5%, MH^+); 173 (50% $C_8H_{10}OS+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{11}H_{16}O_4N_1S_1$ [$M+NH_4^+$]: *m/z* 258.0795 found: *m/z* 258.0791

Anal. *calcd* for $C_{14}H_{16}O_5$; C, 63.6; H, 6.10. Found: C, 63.1; H, 6.06.

Data identical to literature values [2]

4.1.2.6: 5-(2-Methoxy-benzylidene)-2,2-dimethyl- [1,3]-dioxane-4,6-dione (2.75)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2-methoxybenzaldehyde (1.36 g, 10.0 mmol), followed by sodium borohydride (0.73 g, 27.5 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.44 g, 92% yield);

mp (EtOAc) 97-100 °C;

ν_{max} (KBr)/cm^{-1} 3000, 2940, 2886 (C-H); 1772, 1751 (C=O);

δ_H (300 MHz; $CDCl_3$); 7.36 (1H, dd, *J* 7.5, 1.9 Hz, C*H* Ar); 7.25 (1H, td, *J* 7.9, 1.9 Hz, C*H* Ar); 6.93 (1H, td, *J* 7.5, 1.1 Hz, C*H* Ar); 6.85 (1H, d, *J* 7.9 Hz, C*H* Ar); 4.03 (1H, t, *J* 6.0 Hz, C*H*); 3.83 (3H, s, OCH_3); 3.40 (2H, d, *J* 6.0 Hz, CH_2); 1.77 (3H, s, CCH_3); 1.73 (3H, s, CCH_3).

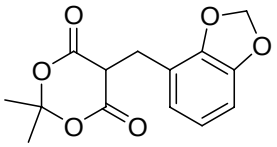
δ_C (75.5 MHz; $CDCl_3$); 170.4; 164.9; 156.7; 131.1; 127.8; 125.3; 120.0; 110.0; 104.4; 54.7; 45.5; 28.0; 27.3.

(EI/CI) *m/z*; 258 ($M+NH_4^+$); 240 (5%, MH^+); 173 (50% $C_8H_{10}OS+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{11}H_{16}O_4N_1S_1$ [$M+NH_4^+$]: *m/z* 258.0795 found: *m/z* 258.0791

Anal. *calcd* for $C_{14}H_{16}O_5$; C, 63.6; H, 6.10. Found: C, 62.8; H, 6.01.

4.1.2.7: 5-Benzo[1,3]dioxol-4-ylmethyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.77)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2-methylenedioxybenzaldehyde (1.50 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.13 g, 73% yield);

mp (EtOAc) 127-128 °C;

ν_{max} (KBr)/cm^{-1} 1755, 1725 (C=O), 1276 (O-C-O);

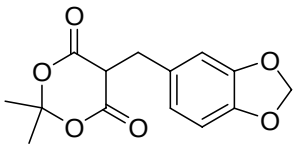
δ_H (300 MHz; $CDCl_3$); 6.81 (1H, d, *J* 2.3 Hz Ar); 6.77 (1H, d, *J* 6.8 Hz, Ar); 6.72 (1H, dd, *J* 6.8 Hz, 2.3 Hz, Ar); 5.93 (2H, s, OC*H*2O); 3.99 (1H, t, *J* 5.7 Hz, C*H*); 3.42 (2H, d, *J* 5.7 Hz, CH_2); 1.80 (3H, s, CCH_3); 1.72 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 165.3, 147.5, 145.6, 123.6, 122.2, 119.4, 107.8, 105.4, 101.0, 46.4, 29.0, 27.1, 26.7.

HRMS (ESI$^+$) *calcd* for $C_{14}H_{14}O_6Na_1$ [M+Na$^+$]: *m/z* 301.0688 found: *m/z* 301.0671

Anal. *calcd* for $C_{14}H_{12}O_6$; C, 60.9; H, 4.40. Found: C, 59.9; H, 4.30.

4.1.2.8: 5-Benzo[1,3]dioxol-5-ylmethyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.78)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), piperonal (1.50 g, 10.0 mmol), followed by sodium borohydride (0.712 g, 27.2 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.16 g, 76% yield);

mp (EtOAc) 114-116 °C;

ν_{max} (KBr)/cm^{-1} 1772, 1751 (C=O); 1256 (O-C-O).

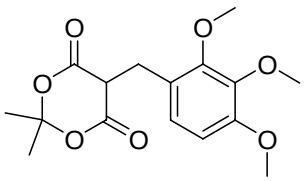
δ_H (300 MHz; $CDCl_3$); 8.31 (1H, s, C*H* Ar); 8.06 (1H, d, *J* 1.9 Hz, C*H* Ar); 7.54 (1H, dd, *J* 8.3 Hz, 1.9 Hz, C*H* Ar); 6.09 (2H, s, OCH_2O); 4.12 (1H, t, *J* 6.1 Hz, C*H*); 3.40 (2H, d, *J* 6.1 Hz, CH_2); 1.76 (3H, s, CCH_3); 1.71 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 164.3, 160.7, 153.6, 148.7, 134.6, 126.8, 111.7, 108.9, 104.7, 102.8, 54.1, 32.7.

HRMS (EI/CI) *calcd* for $C_{14}H_{12}O_6Na_1$ [M+Na^+]: *m/z* 301.0688, found: *m/z* 301.0692.

Anal. *calcd* for $C_{14}H_{12}O_6$; C, 60.9; H, 4.40. Found: C, 60.2; H, 4.37.

4.1.2.9: 2,2-Dimethyl-5-(2,3,4-trimethoxy-benzyl)-[1,3]-dioxane-4,6-dione (2.78)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2,3,4-trimethoxybenzaldehyde (1.96 g, 10.0 mmol), followed by sodium borohydride (0.712 g, 27.2 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.42 g, 79% yield);

mp (EtOAc) 91-94 °C;

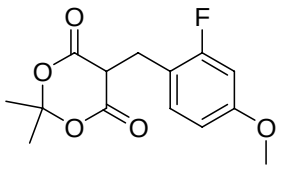
ν_{max} (KBr)/cm^{-1} 2895, 2845, 2828 (C-O-CH_3); 1775, 1742 (C=O);

δ_H (300 MHz; $CDCl_3$); 7.02 (1H, d, *J* 8.7 Hz, C*H* Ar); 6.61 (1H, d, *J* 8.7 Hz, C*H* Ar); 4.03 (1H, t, *J* 5.7 Hz, C*H*); 3.91 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.31 (2H, d, *J* 5.7 Hz, CCH_2); 1.77 (3H, s, CH_3); 1.71 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 165.2, 152.9, 151.6, 141.8, 125.4, 123.4, 107.0, 104.8, 60.7, 60.6, 55.9, 47.4, 28.6, 27.6, 26.5.

HRMS (EI) *calcd* for $C_{16}H_{20}O_7Na$ [M+Na^+]; *m/z* 347.1107, found: *m/z* 347.1100.
Anal. *calcd* for $C_{16}H_{20}O_7$; C, 59.3; H, 6.22. Found: C, 58.8; H, 6.17.

4.1.2.10: 5-(2-fluoro-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.79)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2-fluoro-4-methoxybenzaldehyde (1.54 g, 10.0 mmol), followed by sodium borohydride (0.712 g, 27.2 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.28 g, 82% yield);

mp (EtOAc) 128-130 °C;

ν_{max} (KBr)/cm^{-1} 2840 (C-O-CH_3); 1786, 1744 (C=O); 1514 (C-F);

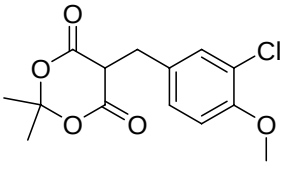
δ_H (300 MHz; $CDCl_3$); 7.23 (1H, t, *J* 8.67 Hz, C*H* Ar); 6.59 (1H, dd, *J* 8.67, 2.64 Hz, C*H* Ar); 6.53 (1H, dd, *J* 12.1, 2.64 Hz, C*H* Ar); 3.72 (1H, t, *J* 6.03 Hz, C*H*); 3.71 (3H, s, OCH_3); 3.32 (2H, d, *J* 6.03 Hz, CH_2); 1.72 (3H, s, CCH_3); 1.64 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 164.9, 163.1 (d, *J* 245.0 Hz, C-F), 159.9 (d, *J* 18.6 Hz), 132.3 (d, *J* 6.02 Hz), 116.2 (d, *J* 21.1 Hz), 109.8, 105.1, 101.7 (d, *J* 25.4 Hz), 55.5, 46.9, 28.6, 26.6, 25.2,

HRMS (ESI^+) *calcd* for $C_{14}H_{15}O_5F_1Na_1$ [$M+Na^+$]: *m/z* 305.0801 found: *m/z* 305.0810

Anal. *calcd* for $C_{16}H_{20}O_7$; C, 59.6; H, 5.36. Found: C, 59.1; H, 5.32.

4.1.2.11: 5-(3-chloro-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.80)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 3-chloro-4-methoxybenzaldehyde (1.70 g, 10.0 mmol), followed by sodium borohydride (0.75 g, 28.3 mmol), were reacted under the standard protocol to generate the desired compound as a cream solid (1.04 g, 63% yield);

mp (EtOAc) 142 °C;

ν_{max} (KBr)/cm^{-1} 2837 (C-O-CH_3); 1784, 1741 (C=O); 7584 (C-Cl);

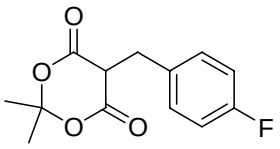
δ_H (300 MHz; $CDCl_3$); 7.35 (1H, s, C*H* Ar); 7.21 (1H, d, *J* 8.3 Hz, C*H* Ar); 6.84 (1H, d, *J* 8.3, C*H* Ar); 3.87 (3H, s, OCH_3); 3.71 (1H, t, *J* 4.9 Hz, C*H*); 3.40 (2H, d, *J* 4.9 Hz, CH_2); 1.75 (3H, s, CCH_3); 1.58 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$); 165.0, 154.1, 131.5, 130.1, 129.3, 122.2, 111.9, 105.2, 56.1, 48.1, 30.8, 28.4, 27.1.

HRMS (ESI^+) *calcd* for $C_{14}H_{15}Cl_1O_5Na_1$ [M+Na^+]: *m/z* 321.0506 found: *m/z* 321.0503

Anal. *calcd* for $C_{14}H_{15}Cl_1O_5$; C, 56.3; H, 5.06. Found: C, 56.0; H, 4.94%

4.1.2.12: 5-(4-fluorobenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.81)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 4-fluorobenzaldehyde (1.24 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a white solid (1.44 g, 97%).

mp (EtOAc) 107-110 °C;

δ_H (300 MHz; $CDCl_3$); 7.33- 7.27 (2H, m, C*H* Ar); 6.97 (2H, t, *J* 8.7 Hz, C*H* Ar); 3.73 (1H, t, *J* 4.9 Hz, C*H*); 3.46 (2H, d, *J* 4.9 Hz, CH_2), 1.79 (3H, s, CCH_3), 1.74 (3H, s, CCH_3);

δ_C NMR (75.5 MHz, $CDCl_3$); 165.1; 163.5 (d, *J* 244.3 Hz, C-F); 160.3; 132.7 (d, *J* 3.4 Hz); 131.5 (d, *J* 7.9 Hz); 115.3 (d, *J* 21.1 Hz); 105.2; 105.2; 48.0; 31.1; 28.3; 27.1

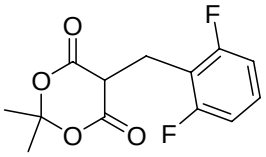
ν_{max} (KBr)/cm^{-1} 3014, 2954, 2893 (C-H); 1786, 1744 (C=O); 1514 (C-F).

HRMS (ESI^+) *calcd* for $C_{13}H_{13}F_1O_6$ Na_1 [M+Na^+]: *m/z* 275.0696 found: *m/z* 275.0690

Anal. *calcd* for $C_{13}H_{13}F_1O_4$: C 61.9, H 5.19; found: C 61.8, H 5.16%

Data identical to literature values [3]

4.1.2.13: 5-(2,6-difluorobenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.82)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2,6-difluorobenzaldehyde (1.42 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a white solid (1.49 g, 98%)

mp (EtOAc) 125-127 °C;

ν_{max} (KBr)/cm^{-1} 3004, 2954, 2909 (C-H); 1782, 1748 (C=O); 1625, 1593 (C-F);

δ_H (300 MHz; $CDCl_3$); 7.26-7.14 (1H, m, Ar); 6.97 (2H, t, *J* 8.3 Hz, C*H* Ar); 3.98 (1H, t, *J* 6.9 Hz, C*H*); 3.43 (2H, d, *J* 6.9 Hz, CH_2); 1.81 (3H, s, CCH_3); 1.77 (3H, s, CCH_3);

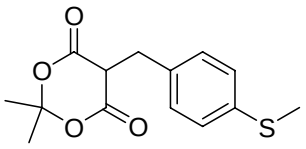
δ_C (75.5 MHz; $CDCl_3$) 164.4; 163.0 (d, *J* 255.0 Hz, C-F); 159.7; 128.5 (t, *J* 10.6 Hz); 113.4 (d, *J* 18.6 Hz); 111.4 (d, *J* 8.1 Hz); 111.1 (d, *J* 8.1 Hz); 105.1; 45,1; 28.5; 26.4; 19.8.

ν_{max} (KBr)/cm^{-1} 3004, 2954, 2909 (C-H); 1782, 1748 (C=O); 1625, 1593 (C-F).

HRMS (EI/CI^+) *calcd* for $C_{13}H_{16}F_2O_4N_1$ [$M+NH_4^+$]: *m/z* 288.1047; found: *m/z* 288.1042;

Anal. *calcd* for $C_{13}H_{12}F_2O_4$: C 57.8, H 4.48; found: C 57.9, H 4.45%

4.1.2.14: 5-(4-(methylthio)benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.83)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 4-thiomethylbenzaldehyde (1.52 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a cream solid (1.34 g, 89%).

mp (EtOAc) 96-98 °C;

ν_{max} (KBr)/cm^{-1} 2996, 2945, 2897, 2875 (C-H); 1789, 1747 (C=O), 1498 (S-CH_3).

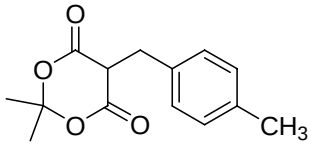
δ_H (300 MHz; $CDCl_3$); 7.25 (2H, d, *J* 6.4 Hz, C*H* Ar); 7.17 (2H, d, *J* 6.4 Hz, C*H* Ar), 3.73 (1H, t, *J* 4.9 Hz, C*H*), 3.44 (3H, s, SCH_3), 3.44 (2H, d, *J* 4.9 Hz, CH_2), 1.73 (3H, s, CCH_3), 1.54 (3H, s, CCH_3).

δ_C (75.5 MHz; $CDCl_3$) 165.1, 137.3, 133.8, 130.3, 126.7, 105.1, 48.1, 31.5, 28.4, 27.2, 15.8.

HRMS (*CI*$^+$) *calcd* for $C_{14}H_{16}O_4Na_1S_1$ [M+Na^+]: *m/z* 303.0662 found: *m/z* 303.0651.

Anal. *calcd* for $C_{14}H_{16}O_4S_1$: C 59.9, H 5.75; found: C 59.9, H 5.72%

4.1.2.15: 2,2-Dimethyl-5-(4-methyl-benzyl)-[1,3]-dioxane-4,6-dione (2.84)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 4-methylbenzaldehyde (1.20 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a white solid (1.51 g, 95%).

mp (EtOAc) 110-112 °C (literature 112-113 °C)[4];

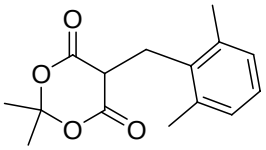
ν_{max} (KBr)/cm^{-1}; 3004, 2942, 2896 (C-H); 1786, 1751 (C=O).

δ_H (300 MHz; $CDCl_3$); 7.19 (2H, d, *J* 7.9 Hz, C*H* Ar); 7.08 (2H, d, *J* 7.9, C*H* Ar); 3.78 (1H, t, *J* 4.9 Hz, *CH*); 3.60 (2H, d, *J* 4.9 Hz, *CH*$_2$), 2.29 (3H, s, CH_3), 1.72 (3H, s, CCH_3), 1.50 (3H, s, CCH_3);

δ_C (75.5 MHz, $CDCl_3$); 165.2, 136.5, 134.0, 129.4, 129.0, 105.0, 47.9, 35.9, 31.4, 28.2, 27.3, 26.9, 20.8.

Data identical to literature values [4]

4.1.2.16: 5-(2,6-dimethylbenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.85)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 2,6-dimethylbenzaldehyde (1.34 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a white solid (1.72 g, 92%).

Mp (EtOAc) 112-115 °C;

ν_{max} (KBr)/cm^{-1} 3000, 2960, 2867 (C-H); 1776, 1739 (C=O).

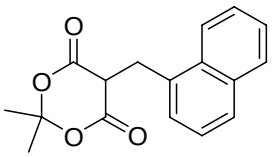
δ_H (300 MHz; $CDCl_3$); 7.13-7.01 (3H, m, C*H* Ar); 3.70 (1H, t, *J* 6.0 Hz, *CH*); 3.50 (2H, d, *J* 6.0 Hz, *CH*$_2$), 2.42 (6H, s, C*H*$_3$), 1.79 (3H, s, CC*H*$_3$), 1.77 (3H, s, CC*H*$_3$).

δ_C (75.5 MHz, $CDCl_3$); 165.0, 137.0, 134.9, 128.6, 126.8, 104.9, 47.0, 28.7, 26.6, 26.4, 20.2.

HRMS (CI^+) *calcd* for $C_{15}H_{18}O_4Na_1$ [M+Na^+]: *m/z* 285.1097 found: *m/z* 285.1091.

Anal. *calcd* for $C_{15}H_{18}O_4$: C 68.6, H 6.92; found: C 68.4, H 6.88%

4.1.2.17: 2,2-dimethyl-5-(naphthalen-1-ylmethyl)-[1,3]-dioxane-4,6-dione (2.86)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), 1-naphthaldehyde (1.56 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol), were reacted under the standard protocol to generate the title compound as a cream solid (1.70 g, 97%).

Mp (EtOAc); 135-137 °C;

IR (KBr)/ cm^{-1} 3057, 3000, 2869 (C-H); 1781, 1750 (C=O).

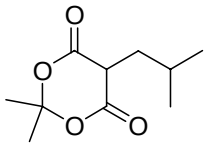
δ_H (300 MHz; $CDCl_3$); 8.08 (1H, d, *J* 8.3 Hz, C*H* Ar); 7.90 (1H, d, *J* 8.3 Hz, C*H* Ar), 7.79 (1H, d, *J* 8.3 Hz, C*H* Ar); 7.65 (1H, d, *J* 7.2 Hz, C*H* Ar); 7.61-7.47 (2H, m, C*H* Ar); 7.44 (1H,

t, *J* 7.2 Hz, C*H* Ar); 3.93 (2H, d, *J* 5.3 Hz, C*H* Ar); 3.81 (1H, t, *J* 5.3 Hz); 1.70 (3H, s, CCH_3); 1.69 (3H, s, CCH_3);

δ_C (75.5 MHz; $CDCl_3$); 165.3; 134.0; 133.9; 131.2; 129.2; 128.4; 127.8; 126.7; 125.7; 125.5; 122.7; 105.1; 47.7; 28.7; 28.6; 26.4.

Data identical to literature values [4]

4.1.2.18: 5-isobutyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (2.87)



2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.25 g, 10.4 mmol), isobutylaldehyde (0.86 g, 10.0 mmol), followed by sodium borohydride (0.71 g, 27.2 mmol),were reacted under the standard protocol to generate the title compound as a white solid (1.05 g, 92%).

mp (EtOAc); 119-120 °C (lit 120 °C).[5]

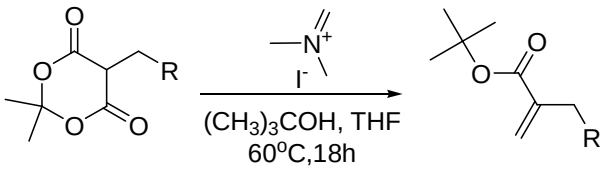
IR (KBr, cm^{-1}) *v* 3003, 2893, 2861 (C-H); 1797, 1748 (C=O).

δ_H (300 MHz, $CDCl_3$); 3.43 (1H, t, *J* 5.7 Hz, C*H*); 1.8-2.15 (3H, m, C*H*$(CH_3)_2$, CH_2 overlap); 1.77 (3H, s, CH_3); 1.72 (3H, s, CH_3); 0.85 (6H, d, *J* 6.0 Hz, CH(CH_3)$_2$);

δ_C (75.5 MHz, $CDCl_3$) δ 165.9; 104.8; 44.1; 35.2; 28.5; 26.7; 25.8; 22.0.

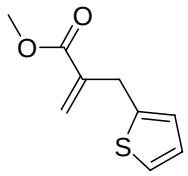
Data identical to literature values [5]

4.1.3 Preparation of 2-benzyl acrylic acid *tert*-butyl esters from 5-monobenzyl alkylidine derivatives.



5-Monobenzyl Meldrum's acid derivative (0.50 g, 2.08 mmol) and dimethyl methylene ammonium iodide (1.00 g, 5.41 mmol) were charged to an oven dried 50 mL round bottomed flask under N_2. The solids were dissolved in tetrahydrofuran (12 mL) and anhydrous *tert*-butanol (12 mL). The reaction mixture was then heated to 65 ºC and stirred for 18 hours. Upon cooling to room temperature the solvent was removed *in vacuo*, and the yellow residue taken up in diethyl ether (25 mL), extracted with saturated sodium bicarbonate (20 mL), 10% aqueous $KHSO_4$ solution (20 mL), saturated sodium chloride solution (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oils were purified via flash column chromatography (petrol: dichloromethane 2:1) to give the title product.

4.1.3.1: 2-Thiophen-2-ylmethyl-acrylic acid methyl ester (2.88)



2,2-Dimethyl-5-thiophen-2-ylmethyl-[1,3]-dioxane-4,6-dione (0.50 g, 2.08 mmol) and dimethyl methylene ammonium iodide (1.24 g, 6.69 mmol), were reacted with methanol (5 mL) under the standard protocol to generate the desired compound as a colourless oil (0.41 g, 88%);

R_f (petrol: dichloromethane 2:1) 0.40.

ν_{max} (neat)/cm^{-1}; 2979, 2931 (C=H_2); 1711 (C=O); 1368 (C-S).

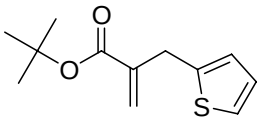
δ_H (300 MHz; $CDCl_3$), 8.0 (1H, dd, *J* 5.3, 1.1 Hz, Ar); 7.0 (1H, dd, *J* 3.4, 5.3 Hz, Ar); 6.82 (1H, dd, *J* 3.4, 1.1 Hz, Ar); 6.16 (1H, s, C*H*H); 5.50 (1H, s, CH*H*); 3.79 (2H, s, CH_2); 3.67 (3H, s, OCH_3).

δ_C (75.5 MHz; $CDCl_3$) 167.4, 141.5, 139.9, 127.3, 126.8, 126.2, 124.5, 52.4, 32.5.

HRMS (ESI^+) *calcd* for $C_{12}H_{17}O_2S_1Na_1$ [$M+Na^+$]: *m/z* 205.02999 found: *m/z* 205.02997.

Data identical to literature values [6]

4.1.3.2: 2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (2.89)



2,2-Dimethyl-5-thiophen-2-ylmethyl-[1,3]-dioxane-4,6-dione (0.50 g, 2.08 mmol) and dimethyl methylene ammonium iodide (1.24 g, 6.69 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.43 g, 92%).

R_f (petrol: dichloromethane 2:1) 0.55.

ν_{max} (neat)/cm^{-1}; 2979, 2931 (C=H_2); 1711 (C=O); 1368 (C-S).

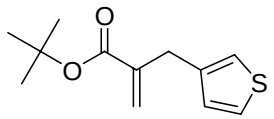
δ_H (300 MHz; $CDCl_3$), 8.0 (1H, dd, *J* 5.3, 1.1 Hz, Ar); 7.0 (1H, dd, *J* 3.4, 5.3 Hz, Ar); 6.82 (1H, dd, *J* 3.4, 1.1 Hz, Ar); 6.16 (1H, s, C*H*H); 5.50 (1H, s, CH*H*); 3.79 (2H, s, CH_2); 1.47 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 165.7, 141.5, 141.0, 126.7, 125.5, 125.3, 123.8, 80.9, 32.2, 27.9.

MS (EI/CI) *m/z;* 242 ($M+NH_4^+$); 225 (25%, MH^+); 186 (50% $C_8H_7O_2S+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{12}H_{17}O_2S_1$ [MH^+]: *m/z* 225.0944 found: *m/z* 225.0943.

4.1.3.3: 2-Thiophen-3-ylmethyl-acrylic acid *tert*-butyl ester (2.90)



2,2-Dimethyl-5-thiophen-3-ylmethyl-[1,3]-dioxane-4,6-dione (0.50 g, 2.08 mmol) and dimethyl methylene ammonium iodide (1.24 g, 6.69 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.41 g, 82%).

R_f (petrol: dichloromethane 2:1) 0.55.

ν_{max} (neat)/cm^{-1}; 2976, 2934 (C=H_2); 1709 (C=O); 1366 (C-S);

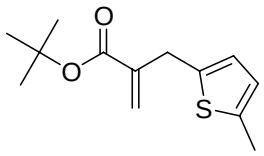
δ_H (300 MHz; $CDCl_3$), 7.23 (1H, dd, *J* 5.0, 3.0 Hz, Ar); 6.97 (1H, s, Ar); 6.91 (1H, dd, *J* 5.0, 1.1 Hz, Ar); 6.12 (1H, s, C*H*H); 5.39 (1H, s, CH*H*); 3.60 (2H, s, CH_2); 1.44 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 165.7, 141.5, 141.0, 126.7, 125.5, 125.3, 123.8, 80.9, 32.2, 27.9;

MS (EI/CI) *m/z*; 242 ($M+NH_4^+$); 225 (20%, MH^+); 186 (60% $C_8H_7O_2S+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{12}H_{17}O_2S_1$ [MH^+]: *m/z* 225.0944 found: *m/z* 225.0943.

4.1.3.4: 2-(3-Methyl-thiophen-2-ylmethyl)-acrylic acid *tert*-butyl ester (2.91)



2,2-Dimethyl-5-((3-methylthiophen-2-yl)methyl)-[1,3]-dioxane-4,6-dione (0.50 g, 1.97 mmol) and dimethyl methylene ammonium iodide (1.05 g, 5.91 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.38 g, 78%).

R_f (petrol: dichloromethane 2:1) 0.5.

ν_{max} (neat)/cm^{-1}; 2977, 2929 (C=H_2); 1712 (C=O); 1392 (C-S).

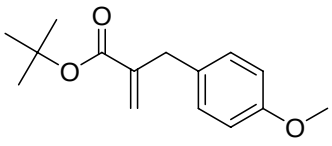
δ_H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, d, *J* 4.9 Hz, Ar), 6.81 (1H, d, *J* 4.9 Hz, Ar), 6.15 (1H, s, CH*H*), 5.33 (1H, s, C*H*H), 3.69 (3H, s, CH_2), 2.14 (3H, s, CH_3), 1.50 (9H, s, C(CH_3)$_3$).

δ_C NMR (75.5 MHz, $CDCl_3$) δ 165.8, 140.4, 134.1, 133.9, 129.9, 124.8, 122.0, 80.8, 29.8, 27.9, 13.5.

MS (EI/CI) *m/z*; 256 (M+NH_4^+); 239 (20%, MH^+); 200 (80% $C_9H_{10}O_2S$+NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{13}H_{18}O_2S_1$ [MH^+]: *m/z* 239.1100 found: *m/z* 239.1099

4.1.3.5: 2-(4-Methoxy-benzyl)-acrylic acid *tert*-butyl ester (2.92)



5-(4-Methoxy-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.89 mmol) and dimethyl methylene ammonium iodide (1.05 g, 5.68 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.45 g, 95%).

R_f (petrol: dichloromethane 2:1) 0.35;

IR (neat, cm^{-1}); 2979 (C=H_2); 1710 (C=O); 1512 (O-CH_3);

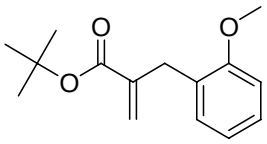
δ_H (300 MHz; $CDCl_3$), 7.10 (2H, d, *J* 6.8, C*H* Ar); 6.82 (2H, d, *J* 6.8 Hz, C*H* Ar); 6.11 (1H, dd, *J* 1.5, 0.75 Hz, C=H_2); 5.40 (1H, dd, *J* 3.4, 1.5 Hz, C=H_2); 3.79 (3H, s, OCH_3); 3.53 (2H, s, CH_2); 1.44 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 167.1, 158.0, 142.1, 131.1, 129.9 (2C), 129.7 124.8, 113.7, 80.6, 55.2, 37.3, 28.0;

MS (EI/CI) *m/z*; 282 ($M+NH_4^+$); 266 (80 % MH^+); 210 (50% $C_{11}H_{12}O_3+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{15}H_{24}O_3N_1$ [$M+NH_4^+$]: *m/z* 266.1751 found: *m/z* 266.1750.

4.1.3.6: 2-(2-Methoxy-benzyl)-acrylic acid *tert*-butyl ester (2.93)



5-(2-Methoxy-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.89 mmol) and dimethyl methylene ammonium iodide (0.875 g, 4.73 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.43 g, 94%).

R_f (petrol: dichloromethane 2:1) 0.35;

IR (neat, cm^{-1}); 2979 (C=H_2); 1711 (C=O); 1493 (O-CH_3);

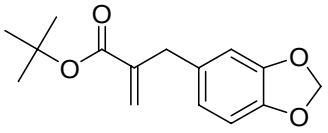
δ_H (300 MHz; $CDCl_3$), 7.21 (1H, td, *J* 7.9, 1.5 Hz, C*H* Ar); 7.12 (1H, dd, *J* 7.5, 1.5 Hz, C*H* Ar); 6.89 (1H, td, *J* 7.5, 1.1 Hz, C*H* Ar); 6.86 (1H, d, *J* 7.9 Hz, C*H* Ar); 6.10 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 5.26 (1H, dd, *J* 3.4, 1.5 Hz, C=H_2); 3.80 (3H, s, OCH_3); 3.59 (2H, s, CH_2); 1.47 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$) 167.2, 157.4, 140.9, 130.4, 127.5, 126.8, 124.5, 120.3, 110.3, 80.4, 55.2, 31.9, 28.0;

MS (EI/CI) *m/z*; 282 ($M+NH_4^+$); 266 (80 % MH^+); 210 (50% $C_{11}H_{12}O_3+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{15}H_{24}O_3N_1$ [$M+NH_4^+$]: *m/z* 266.1751 found: *m/z* 266.1749.

4.1.3.7: 2-Benzo[1,3]dioxol-5-ylmethyl-acrylic acid *tert*-butyl ester (2.94)



5-Benzo[1,3]dioxol-5-ylmethyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.51 g, 1.83 mmol) and dimethyl methylene ammonium iodide (0.961 g, 5.20 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.43 g, 90%)

R_f (petrol: dichloromethane 1:1) 0.35;

ν_{max} (neat)/cm^{-1}; 1712 (C=O), 1247 (O-C-O);

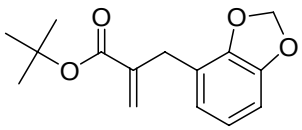
δ_H (300 MHz; $CDCl_3$), 6.81 (1H, s, C*H* Ar); 6.72 (1H, dd, *J* 7.5, 1.9 Hz, C*H* Ar); 6.61 (1H, dd, *J* 8.3 Hz, 1.9 Hz, C*H* Ar); 6.19 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 5.87 (2H, s, OCH_2O); 5.43 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 3.54 (2H, s, CH_2); 1.45 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 165.9, 148.7, 145.8, 139.8, 130.8, 125.0, 122.4, 120.4, 115.2, 100.4, 80.5, 31.4, 27.9.

MS (EI/CI) *m/z*; 280 ($M+NH_4^+$); 262 (25 % MH^+); 224 (60% $C_{11}H_{10}O_4+NH_4^+$);

HRMS (ESI^+) *calcd* for $C_{15}H_{18}O_4Na_1$ [$M+Na^+$]: *m/z* 285.1103 found: *m/z* 285.1101

4.1.3.8: 2-Benzo[1,3]dioxol-4-ylmethyl-acrylic acid *tert*-butyl ester (2.95)



5-Benzo[1,3]dioxol-5-ylmethyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.51 g, 1.83 mmol) and dimethyl methylene ammonium iodide (0.961 g, 5.20 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.41 g, 87%)

R_f (petrol:dichloromethane 1:1) 0.35;

ν_{max} (neat)/cm^{-1}; 1708 (C=O), 1251 (O-C-O);

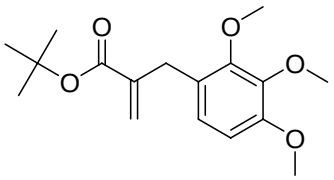
δ_H (300 MHz; $CDCl_3$), 6.74 (1H, dd, *J* 15.1, 7.5 Hz, C*H* Ar); 6.70 (1H, dd, *J* 7.5, 1.5 Hz, C*H* Ar); 6.66 (1H, dd, *J* 7.5, 1.5 Hz, C*H* Ar); 6.16 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 5.91 (2H, s, OCH_2O); 5.39 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 3.56 (2H, s, CH_2); 1.46 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 165.9, 147.0, 145.5, 139.8, 125.0, 122.8, 121.2, 120.4, 106.7, 100.4, 80.5, 31.4, 27.9.

MS (EI/CI) *m/z*; 280 ($M+NH_4^+$); 262 (25 % MH^+); 224 (60% $C_{11}H_{10}O_4+NH_4^+$);

HRMS (ESI^+) *calcd* for $C_{15}H_{18}O_4Na_1$ [$M+Na^+$]: *m/z* 285.1103 found: *m/z* 285.1091

4.1.3.9: *tert*-butyl 2-(2,3,4-trimethoxybenzyl)acrylate (2.96)



5-(2,3,4-Trimethoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.54 mmol) and dimethyl methylene ammonium iodide (0.856 g, 4.62 mmol), were reacted under the standard protocol to generate the title compound as a yellow oil (0.42 g, 88%);

R_f (dichloromethane) 0.3;

IR (neat, cm^{-1}); 2976, 2937 (C=H_2); 1712 (C=O) 1627, 1618 (O-CH_3);

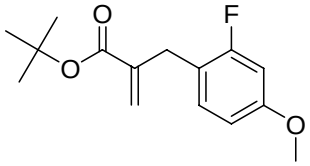
δ_H (300 MHz; $CDCl_3$), 6.80 (1H, d, *J* 8.7, C*H* Ar); 6.60 (H, d, *J* 8.7 Hz, C*H* Ar); 6.14 (1H, dd, *J* = 2.6, 1.1 Hz, C=H_2); 5.38 (1H, dd, *J* 3.4, 1.5 Hz, C=H_2); 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.53 (2H, s, CH_2); 1.46 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 166.3, 152.3, 151.9, 142.2, 141.6, 125.0, 124.5, 124.4, 107.0, 80.5, 60.8, 60.6, 55.9, 31.6, , 28.0.

MS (EI/CI) *m/z*; 326 ($M+NH_4^+$); 309 (10 % MH^+); 210 (80% $C_{13}H_{16}O_5+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{17}H_{25}O_3N_1$ [M+H]: *m/z* 309.1697 found: *m/z* 309.1698.

4.1.3.10: 2-(2-Fluoro-4-methoxy-benzyl)-acrylic acid *tert*-butyl ester (2.97)



5-(2-fluoro-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.77 mmol) and dimethyl methylene ammonium iodide (0.875 g, 4.73 mmol), were reacted under the standard protocol to generate the desired compound as a light yellow oil (0.39 g, 83%).

R_f (petrol: dichloromethane 2:1) 0.35;

ν_{max} (neat)/cm^{-1}; 2978 (C=H_2); 1708 (C=O); 1627 (O-CH_3); 1509 (C-F);

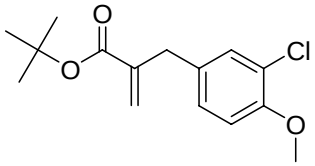
δ_H (300 MHz; $CDCl_3$), 7.06 (1H, t, *J* 8.7 Hz, C*H* Ar); 6.60 (1H, dd, *J* 8.7, 2.6 Hz, C*H* Ar); 6.51 (1H, s, C*H* Ar); 6.12 (1H, dd, *J* 2.6, 1.1 Hz, C=H_2); 5.32 (1H, dd, *J* 1.5, 0.74 Hz, C=H_2); 3.76 (3H, s, OCH_3); 3.53 (2H, s, CH_2); 1.45 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 165.9, 163.0 (d, *J* 266.0 Hz, C-F), 159.5 (d, *J* 20.5 Hz), 140.4, 131.3 (d, *J* 6.82 Hz), 124.8, 117.5 (d, *J* 16.1 Hz), 109.5, 101.5, 80.6, 55.3, 30.3, 27.9;

MS (EI/CI) *m/z*; 284 (M+NH_4^+); 266 (20 % MH^+); 228 (70% $C_{11}H_{11}F_1O_3$+NH_4^+);

HRMS (ESI^+) *calcd* for $C_{15}H_{19}O_3F_1Na_1$ [M+Na^+]: *m/z* 289.1216 found: *m/z* 289.1204

4.1.3.11: 2-(3-Chloro-4-methoxy-benzyl)-acrylic acid *tert*-butyl ester (2.98)



5-(3-chloro-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.67 mmol) and dimethyl methylene ammonium iodide (0.875 g, 4.73 mmol), were reacted under the standard protocol to generate the desired compound as a yellow oil (0.43 g, 91%);

R_f (petrol: dichloromethane 2:1) 0.30;

ν_{max} (neat)/cm^{-1}; 2979 (C=H_2); 1711 (C=O); 1590 (O-CH_3) 756 (C-Cl);

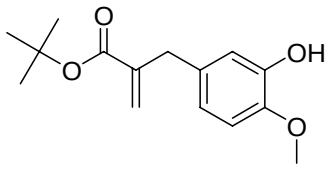
δ_H (300 MHz; $CDCl_3$), 7.17 (1H, d, *J* 2.3 Hz; C*H* Ar); 7.02 (1H, dd, *J* 8.3, 2.3 Hz, C*H* Ar); 6.82 (1H, d, *J* 8.3 Hz, C*H* Ar); 6.12 (1H, dd, *J* 1.5, 0.75 Hz, C=H_2); 5.37 (1H, dd, *J* 3.0, 1.5 Hz, C=H_2); 3.84 (3H, s, OCH_3); 3.48 (2H, s, CH_2); 1.42 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$) 165.8, 153.3, 141.3, 132.1, 130.5, 128.0, 125.1, 121.9, 111.8, 80.6, 55.9, 37.0, 27.8;

MS (EI/CI) *m/z*; 300 (M+NH_4^+); 282 (10% MH^+); 244 (80% $C_{11}H_{11}Cl_1O_3$+NH_4^+);

HRMS (ESI^+) *calcd* for $C_{15}H_{19}Cl_1O_3Na_1$ [M+Na^+]: *m/z* 305.0920 found: *m/z* 305.0919

4.1.3.12: 2-(3-Hydroxy-4-methoxy-benzyl)-acrylic acid *tert*-butyl ester (2.99)



5-(3-hydroxy-4-methoxybenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.79 mmol) and dimethyl methylene ammonium iodide (0.875 g, 4.73 mmol), were reacted under the standard protocol to generate the desired compound as a white semisolid (0.27 g, 57% yield);

R_f (petrol: dichloromethane 2:1) 0.20;

mp (Hexanes) 41-43 °C;

ν_{max} (neat)/cm^{-1}; 2979 (C=H_2); 1711 (C=O); 1493 (O-CH_3);

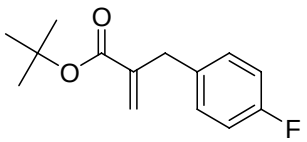
δ_H (300 MHz; $CDCl_3$), 6.84 (1H, dd, *J* 7.2, 1.1 Hz, C*H* Ar); 6.70 (1H, s, C*H* Ar); 6.68 (1H, dd, *J* 7.2, 1.9 Hz, C*H* Ar); 6.12 (1H, dd, *J* = 1.5, 0.75 Hz, C=H_2); 5.37 (1H, dd, *J* = 3.0, 1.5 Hz, C=H_2); 3.85 (3H, s, OCH_3); 3.53 (2H, s, CH_2); 1.46 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$) 166.2, 146.3, 143.9, 142.0, 130.8, 124.7, 121.6, 114.1, 111.4, 80.6, 55.7, 37.7, 27.9.

MS (EI/CI) *m/z*; 282 (M+NH_4^+); 264 (15% MH^+); 208 (50% $C_{11}H_{12}O_4$+NH_4^+);

HRMS (ESI^+) *calcd* for $C_{15}H_{20}O_4Na_1$ [M+Na^+]: *m/z* 287.1259 found: *m/z* 287.1258

4.1.3.13: 2-(4-Fluoro-benzyl)-acrylic acid *tert*-butyl ester (2.100)



5-(4-Fluoro-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.52 g, 2.20 mmol) and dimethyl methylene ammonium iodide (0.925 g, 5.00 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.46 g, 84% yield).

R_f (petrol: dichloromethane 2:1) 0.55;

IR (neat, cm^{-1}); 2983, 3052 (C=H_2); 1712 (C=O); 1510 (C-F);

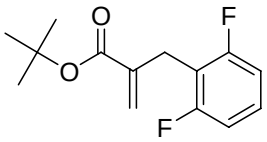
δ_H (300 MHz; $CDCl_3$), 7.14 (2H, dd, *J* 8.7, 5.7 Hz, C*H* Ar), 6.97 (2H, t, *J* 8.7 Hz, C*H* Ar); 6.14 (1H, dd, *J* 1.5, 0.75 Hz, C=H_2); 5.37 (1H, dd, *J* 3.0, 1.5 Hz, C=H_2); 3.56 (2H, s, CH_2); 1.35 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$); 165.9, 163.0, 159.8, 141.5, 134.6, 130.3, 130.2, 125.2, 115.1, 114.9, 80.7, 37.4, 27.9.

MS (EI/CI) *m/z*; 254 ($M+NH_4^+$); 237 (15 % MH^+); 198 (50% $C_{10}H_9F_1O_2+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{14}H_{21}O_2F_1N_1$ [$M+NH_4^+$]: *m/z* 254.1551 found: *m/z* 254.1551

4.1.3.14: 2-(2,6-Difluoro-benzyl)-acrylic acid *tert*-butyl ester (2.101)



5-(2,6-Difluoro-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.52 g, 2.20 mmol) and dimethyl methylene ammonium iodide (0.925 g, 5.00 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.46 g, 84% yield).

R_f (petrol: dichloromethane 2:1) 0.6;

IR (neat, cm^{-1}); 2980, 2934 (C=H_2); 1712 (C=O); 1594, 1470 (C-F);

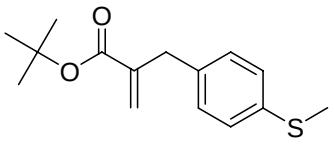
δ_H (300 MHz; $CDCl_3$), 7.26-7.14 (1H, m, Ar); 6.97 (2H, t, *J* 7.6 Hz, C*H* Ar); 6.12 (1H, d, *J* 1.1 Hz, C=H_2); 5.19 (1H, d, *J* 0.75 Hz, C=H_2); 3.64 (2H, s, CH_2); 1.49 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$); 165.7, 163.2, 159.9, 138.8, 128.3, 124.3, 114.8, 111.0, 80.9, 27.9, 24.5;

MS (EI/CI) *m/z*; 272 ($M+NH_4^+$); 255 (10 % MH^+); 216 (60% $C_{10}H_8F_2O_2+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{14}H_{20}O_2F_2N_1$ [$M+NH_4^+$]: *m/z* 272.1457 found: *m/z* 272.1459.

4.1.3.15: 2-(4-Methylsulfanyl-benzyl)-acrylic acid *tert*-butyl ester (2.102)



5-(4-(methylthio)benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.78 mmol) and and dimethyl methylene ammonium iodide (1.01 g, 5.35 mmol), were reacted under the standard protocol to generate the title compound as a yellow oil (0.46 g, 98%).

R_f (petrol: dichloromethane 2:1) 0.4;

IR (neat, cm^{-1}); 2978, 2934 (C=H_2); 1712 (C=O); 1137 (C-S);

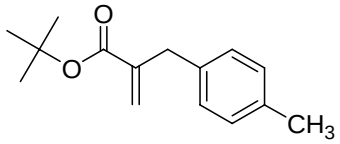
δ_H (300 MHz, $CDCl_3$); 7.20 (2H, d, *J* 8.3, C*H* Ar); 6.11 (2H, d, *J* 8.3 Hz, C*H* Ar); 6.14 (1H, d, *J* 1.5, 0.75 Hz, C=H_2); 5.38 (1H, dd, *J* 3.0, 1.5 Hz, C=H_2); 3.53 (2H, s, CH_2); 2.46 (3H, s, SCH_3); 1.42 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz, $CDCl_3$) 166.0, 141.5, 136.1, 135.8, 129.4 (2C), 126.9, 125.1, 80.6, 53.3, 37.6, 27.9, 16.1.

MS (EI/CI) *m/z*; 282 ($M+NH_4^+$); 265 (80 % MH^+); 226 (50% $C_{11}H_{12}O_2S_1+NH_4^+$);

HRMS (EI/CI$^+$) *calcd* for $C_{15}H_{20}O_2S_1$ [$M+H^+$]: *m/z* 265.1257 found: *m/z* 265.1255

4.1.3.16: 2-(4-Methyl-benzyl)-acrylic acid *tert*-butyl ester (2.103)



5-(4-methyl-benzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 2.01 mmol) and dimethyl methylene ammonium iodide (1.08 g, 6.04 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.38 g, 82%).

R_f (petrol: dichloromethane 2:1) 0.65.

ν_{max} (neat)/cm^{-1} 2971, 2964 (C=H_2); 1704.1 (C=O).

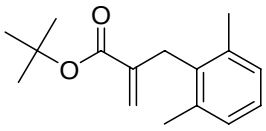
δ_H (300 MHz; $CDCl_3$), 7.15-7.06 (4H, m, Ar); 6.13 (1H, dd, *J* 1.5, 0.75 Hz C=H_2); 5.36 (1H, dd, *J* 3.0, 1.5 Hz C=H_2); 3.56 (2H, s, CH_2); 2.33 (3H, s, CH_3); 1.45 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$); 166.2, 141.9, 135.9, 135.5, 128.9, 128.8, 124.9, 80.5, 37.6, 27.9, 20.9.

(EI/CI) *m/z*; 250 (M+NH_4^+); 233 (8%, MH^+); 194 (60% $C_{11}H_{16}O_2$+NH_4^+);

HRMS (CI^+) *calcd* for $C_{15}H_{24}O_2N_1$ [M+NH_4^+]: *m/z* 250.1807 found: *m/z* 250.1802.

4.1.3.17: 2-(2,6-Dimethyl-benzyl)-acrylic acid *tert*-butyl ester (2.104)



5-(2,6-dimethylbenzyl)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.91 mmol) and dimethyl methylene ammonium iodide (1.06 g, 5.72 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.40 g, 85%).

R_f (petrol: dichloromethane 3:1) 0.5;

IR (neat, cm^{-1}); 2978, 2964 (C=H_2); 1708 (C=O).

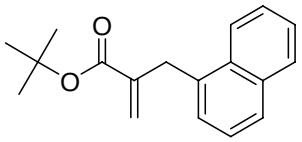
δ_H (300 MHz, $CDCl_3$) 7.12-7.00 (3H, m, Ar); 6.02 (1H, dd, *J* 3.4, 1.9 Hz, C=H_2); 4.85 (1H, dd, *J* 3.8, 1.9 Hz, C=H_2); 3.59 (2H, s, CH_2); 2.33 (6H, s, CH_3); 1.56 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz, $CDCl_3$) 166.5, 139.3, 137.0, 135.4, 127.9, 126.3, 123.0, 80.7, 31.1, 28.0, 19.7.

(EI/CI) *m/z*; 264.2 ($M+NH_4^+$); 247 (5%, MH^+); 208 (70% $C_{12}H_{14}O_2+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{16}H_{26}O_2N_1$ [$M+NH_4^+$]: *m/z* 264.1958 found: *m/z* 264.1959.

4.1.3.18: 2-Naphthalen-1-ylmethyl-acrylic acid *tert*-butyl ester (2.105)



2,2-Dimethyl-5-naphthalen-1-ylmethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.76 mmol) and dimethyl methylene ammonium iodide (0.875 g, 4.73 mmol), were reacted under the standard protocol to generate the desired compound as orange oils (0.43 g, 92% yield);

R_f (petrol: dichloromethane 3:1) 0.55;

ν_{max} (neat)/cm^{-1}; 2978 ($C=H_2$); 1711 (C=O);

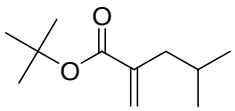
δ_H (300 MHz, $CDCl_3$); 7.96-7.89 (1H, m, C*H* Ar), 7-89-7.83 (1H, m, C*H* Ar), 7.77 (1H, d, *J* 8.3 Hz, C*H* Ar), 7.53-7.44 (2H, m, C*H* Ar), 7.42 (1H, d, *J* 8.3 Hz, C*H* Ar), 7.34 (1H, d, *J* 7.2 Hz, C*H* Ar), 6.14 (1H, dd, *J* 2.6, 1.5 Hz, C=H_2), 5.10 (1H, dd, *J* 3.0, 1.5 Hz, C=H_2), 4.06 (2H, s, CH_2), 1.51 (9H, s, C(CH_3)$_3$).

δ_C (75.5 MHz; $CDCl_3$) 166.4, 140.9, 135.0, 133.8, 131.9, 129.1, 128.6, 127.3, 125.8, 125.5, 125.4, 125.2, 124.2, 80.8, 34.7, 28.0.

(EI/CI) *m/z*; 286 ($M+NH_4^+$); 269 (3%, MH^+); 230 (75% $C_{14}H_{12}O_2+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{18}H_{21}O_2$ [$M+H^+$]: *m/z* 269.1536 found: *m/z* 269.1538.

4.1.3.19: 4-Methyl-2-methylene-pentanoic acid *tert*-butyl ester (2.106)



5-isobutyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (0.50 g, 1.91 mmol) and dimethyl methylene ammonium iodide (1.06 g, 5.72 mmol), were reacted under the standard protocol to generate the title compound as a colourless oil (0.348 g, 98%).

R_f (petrol: dichloromethane 4:1) 0.55;

ν_{max} (neat)/cm^{-1}; 2959 (C=H_2); 1710 (C=O);

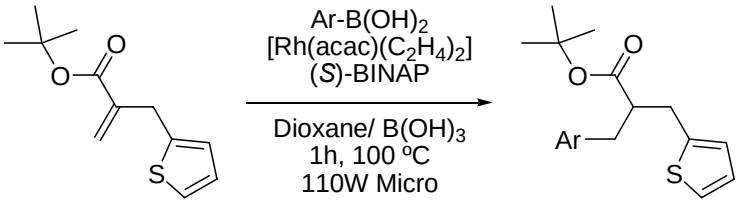
δ_H (300 MHz; $CDCl_3$); 6.05 (1H, d, *J* 1.9 Hz, C=H_2), 5.39 (1H, dd, *J* 1.9, 1.1, Hz C=H_2), 2.13 (2H, dd *J* 6.8, 1.1 Hz, CH_2), 1.77 (1H, tsep, *J* 6.8, 3.4 Hz, CH(CH_3)$_2$), 1.48 (9H, s, C(CH_3)$_3$), 0.88 (6H, d, *J* 6.4, CH(CH_3)$_2$).

δ_C (75.5 MHz; $CDCl_3$) 167.2; 141.8; 125.0; 80.7; 41.8; 28.5; 27.8; 22.7.

(EI/CI) *m/z*; 202 (M+NH_4^+); 184 (5%, MH^+); 146 (50% $C_7H_{12}O_2$+NH_4^+);

HRMS (CI^+) *calcd* for $C_{11}H_{24}O_2N_1$ [M+NH_4^+]: *m/z* 202.1802 found: *m/z* 202.1803.

4.1.4: General preparation of α- α substituted 3-Benzyl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl esters



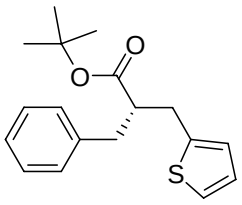
***via* heating methods (Method A):**

A 24 mL screw-capped vial equipped with a rubber septum was charged with *tert*-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), phenyl boronic acid (0.098 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol). Dioxane (2 mL) and water (0.2 mL) were added *via* syringe under a stream of argon. The mixture was subsequently degassed for 5 minutes before being transferred with to a preheated hotplate at 100 °C for 20 h. The crude reaction mixture was diluted with diethyl ether (5 mL), filtered through a short plug of silica gel (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to give the title product.

***via* microwave irradiation (Method B):**

A 10 mL microwave tube equipped with a rubber septum was charged with *tert*-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), phenyl boronic acid (0.098 g, 0.80 mmol), acetylacetonatobis(ethylene)rhodium (I) (0.003 g, 0.008 mmol), (*S*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.007 g, 0.012 mmol) and boric acid (0.040 g, 0.80 mmol). Dioxane (2 mL) was added by syringe and the vessel was purged with argon for 5 minutes. The mixture was transferred to the microwave reactor (conditions; 110W, 100 ^{o}C) for 1 h. The crude reaction mixture was taken up in diethyl ether (5 mL), filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to yield the title product.

4.1.4.1: 3-Phenyl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.107)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol), phenyl boronic acid (0.138 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless oil (0.052 g, 91% yield);

R_f (petrol:dichloromethane, 2:1); 0.4

$[\alpha]_D^{20}$ = -4.6 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 3008, 2980 (C-H); 1723 (C=O); 1147 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.38-7.22 (5H, m, Ar), 7.18 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.18 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.86 (1H, d, *J* 3.4 Hz, C*H* thiophene); 3.28- 3.15 (1H, m, C*H*); 3.09- 2.81 (4H, m, CH_2, CH_2); 1.32 (9H, s, $C(CH_3)_3$);

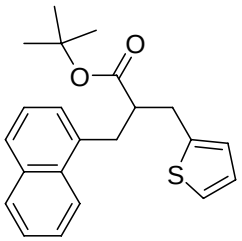
δ_C (75.5 MHz; $CDCl_3$); 173.7, 141.7, 139.0, 129.1, 128.3, 126.6, 126.3, 125.6, 123.7, 80.5, 50.3, 38.2, 32.2, 27.8.

MS (EI/CI) *m/z*; 320 (45% $M+NH_4^+$); 303.2 (5%, MH^+); 264 (50% $C_{14}H_{14}O_2S+NH_4^+$);

HRMS (CI) *calcd* for $C_{18}H_{26}O_2N_1S_1$ [$M+NH_4^+$] *m/z* 320.1675 found: *m/z* 320.1679;

HPLC Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 8.71 (*R*) and 9.30 (*S*).

4.1.4.2: 3-Naphthalen-1-yl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.108)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol), 1-naphthyl boronic acid (0.138 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless oil (0.066 g, 94% yield);

R_f (petrol:dichloromethane, 2:1); 0.35;

ν_{max} (neat)/cm^{-1}; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH_3); 1148 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.94 (1H, d, *J* 7.2 Hz, Ar); 7.86 (1H, d, *J* 7.9 Hz, Ar); 7.74 (1H, dd, *J* 7.5, 1.8 Hz, Ar); 7.54- 7.44 (2H, m, Ar); 7.54- 7.42- 7.32 (2H, m, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* Thiophene); 6.92 (1H, dd, *J* 5.3, 3.4 Hz, C*H* Thiophene); 6.84 (1H, dd, *J* 3.4, 0.75 Hz, C*H* Thiophene); 3.46- 3.34 (1H, m, C*H*); 3.33- 3.21 (2H, m, CH_2); 3.13- 2.98 (2H, m, CH_2); 1.22 (9H, s, C(CH_3)$_3$);

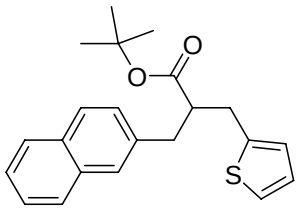
δ_C (75.5 MHz; $CDCl_3$); 173.1, 143.3, 133.5, 126.9, 126.6, 126.5, 126.3, 125.8, 125.6, 125.1, 124.3, 124.3, 124.2, 123.0, 82.4, 48.4, 38.2, 32.3, 29.9, 28.8.

MS (EI/CI) *m/z*; 352 (10% MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{22}H_{24}O_2S_1$ [M+H^+] *m/z* 353.1570 found: *m/z* 353.1569

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 11.01 (*R*) and 16.30 (*S*).

4.1.5.3: 3-Naphthalen-2-yl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.109)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol), 2-naphthyl boronic acid (0.138 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless oil (0.066 g, 94% yield);

R_f (petrol:dichloromethane, 2:1); 0.35

$[\alpha]_D^{20}$ = -5.8 º (*c*=0.12, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH_3); 1148 (C-S);

δ_H (400 MHz; $CDCl_3$), 7.87 (1H, d, *J* 8.1 Hz, Ar); 7.83 (2H, d, *J* 8.1 Hz, Ar); 7.70 (1H, s, Ar); 7.57- 7.46 (2H, m, Ar); 7.40 (1H, d, *J* 8.6 Hz, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.92 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.46- 3.34 (1H, m, C*H*); 3.33- 3.21 (1H, m, CH_2); 3.13- 2.98 (3H, m, CH_2); 1.22 (9H, s, C(CH_3)$_3$);

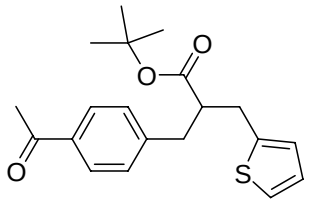
δ_C (75.5 MHz; $CDCl_3$); 173.8, 141.7, 136.6, 133.5, 132.3, 128.0, 127.9, 127.6, 126.7, 126.0, 125.9, 125.7, 125.4, 123.8, 80.7, 50.3, 38.4, 32.3, 27.9, 23.8

MS (EI/CI) *m/z*; 352 (10% MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{22}H_{24}O_2S_1$ [M+H^+] *m/z* 353.1570 found: *m/z* 353.1569

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 10.35 (*R*) and 11.04 (*S*).

4.1.4.4: 3-(4-Acetyl-phenyl)-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.110)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-acetylphenylboronic acid (0.132 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.047 g, 68% yield);

R_f (petrol:dichloromethane, 2:1); 0.1;

$[\alpha]_D^{20}$ = -4.0 º (*c*=0.90, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 3008, 2980 (C-H); 1723 (C=O); 1147 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.80 (2H, d, *J* 8.7 Hz, Ar); 7.20 (2H, d, *J* 8.7 Hz, Ar); 7.07 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.83 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.74 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.17-3.02 (1H, m, C*H*); 2.97-2.73 (4H, m, CH_2, CH_2); 2.51 (3H, s, C(O)CH_3); 1.32 (9H, s, C(CH_3)$_3$).

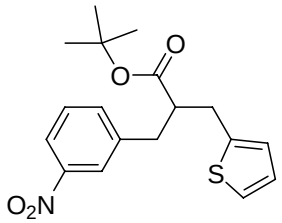
δ_C (75.5 MHz; $CDCl_3$); 197.7, 173.2, 144.7, 141.1, 135.3, 129.1, 128.3, 126.6, 125.7, 123.8, 80.7, 49.8, 37.8, 32.2, 27.7, 26.5.

MS (EI/CI) *m/z*; 320 (45% M+NH_4^+); 303.2 (5%, MH^+); 264 (50% $C_{14}H_{14}O_2S$+NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{18}H_{26}O_2N_1S_1$ [M+NH_4^+] *m/z* 320.1675 found: *m/z* 320.1679;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 20.1 (*R*) and 25.1 (*S*).

4.1.4.5: 2-(3-Nitro-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.111)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 3-nitro phenylboronic acid (0.133 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.052 g, 79% yield);

R_f (petrol:dichloromethane, 1:2); 0.2

ν_{max} (neat)/cm^{-1}; 2977, 292 (C-H); 1723 (C=O); 1530 (N-O); 1151 (C-S);

δ_H (300 MHz; $CDCl_3$), 8.0 (1H, d, *J* 8.7 Hz, Ar); 7.98 (1H, s, *J* 8.0 Hz, Ar); 7.44 (1H, d, *J* 7.9 Hz, Ar); 7.36 (1H, d, *J* 7.9 Hz, Ar); 7.18 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.18 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.86 (1H, d, *J* 3.4 Hz, C*H* thiophene); 3.19-3.09 (1H, m, C*H*); 2.99-2.78 (4H, m, CH_2, CH_2); 1.19 (9H, s, C(CH_3)$_3$);

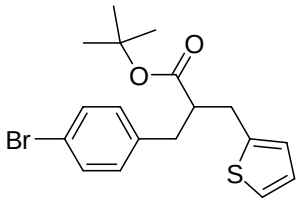
δ_C (75.5 MHz; $CDCl_3$); 172.9, 141.1, 140.8, 135.3, 129.1, 126.7, 125.9, 124.0, 123.8, 121.5, 81.1, 49.9, 37.4, 32.4, 27.8.

MS (EI/CI) *m/z*; 365 (45% M+NH_4^+); 335 (20%, MH^+);

HRMS (ESI^+) *calcd* for $C_{18}H_{25}O_4N_2S_1$ [M+NH_4^+] *m/z* 365.1530 found: *m/z* 365.1527;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 10.6 (*R*) and 14.1 (*S*).

4.1.4.6: 2-(4-Bromo-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.112)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-bromophenylboronic acid (0.161 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.058 g, 76% yield);

R_f (petrol:dichloromethane, 2:1); 0.36

$[\alpha]_D^{20}$ = -5.1 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2978, 2930 (C-H); 1724 (C=O); 1488 ($CO-CH_3$) 1367 ($C-CH_3$); 1151 (C-S); 550 (C-Br);

δ_H (400 MHz; $CDCl_3$), 7.39 (2H, d, *J* 8.6 Hz, Ar); 7.14 (1H, dd, *J* 5.1, 1.3 Hz, C*H* thiophene); 7.06 (2H, d, *J* 8.6 Hz, Ar); 6.91 (1H, dd, *J* 5.1, 3.5 Hz, C*H* thiophene); 6.91 (1H, dd, *J* 3.5, 1.3 Hz, C*H* thiophene); 3.22-3.10 (1H, m, C*H*); 3.05- 2.70 (4H, m, CH_2); 1.28 (9H, s, $C(CH_3)_3$);

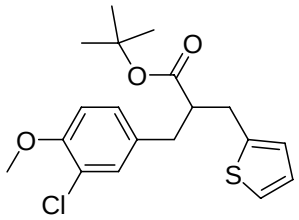
δ_C (75.5 MHz; $CDCl_3$); 173.3, 141.3, 140.8, 138.0, 131.3, 131.2, 130.7, 126.6, 125.6, 123.7, 120.1, 80.7, 50.0, 37.4, 32.2, 27.8;

MS (EI/CI) *m/z*; 381 (80% MH^+);

HRMS (CI^+) *calcd* for $C_{18}H_{25}N_1BrO_2S$ [$M+NH_4^+$] *m/z* 381.3271 found: *m/z* 381.3274

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 8.31 (*R*) and 8.72 (*S*).

4.1.4.7: 2-(3-Chloro-4-methoxy-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.113)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol), 3-chloro-4-methoxyphenylboronic acid (0.149 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.059 g, 81% yield);

R_f (petrol:dichloromethane, 2:1) 0.1;

$[\alpha]_D^{20}$ = -4.3 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2993, 2871 (C-H); 1720 (C=O); 1389, 1262 (C-CH_3); 1150 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.20 (1H, d, *J* 2.3 Hz, Ar); 7.14 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.03 (1H, dd, *J* 8.3, 2.3 Hz, Ar); 6.91 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.85-6.79 (2H, m, Ar); 3.87 (3H, s, OCH_3); 3.22-3.08 (1H, m, C*H*); 3.04- 2.64 (4H, m, CH_2); 1.28 (9H, s, C(CH_3)$_3$);

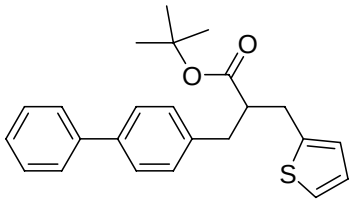
δ_C (75.5 MHz; $CDCl_3$); 173.4, 153.4, 141.3, 132.0, 130.6, 128.2, 126.6, 125.6, 123.7, 121.9, 111.8, 80.7, 56.0, 50.3, 36.9, 32.1, 27.8;

MS (EI/CI) *m/z*; 359 (85% M-NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{27}N_1Cl_1O_3S_1$ [M+NH_4^+] *m/z* 384.1395 found: *m/z* 384.1396

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 12.50 (*R*) and 13.41 (*S*).

4.1.4.8: 3-Biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.125)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester, (0.045 g, 0.20 mmol) and 4-biphenyl boronic acid (0.158 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless semi-solid (0.058 g, 76% yield);

R_f (petrol:dichloromethane, 2:1); 0.3

mp (Hexanes) 38-40 °C

$[\alpha]_D^{20}$ = -4.9 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2930, 3029 (C-H); 1724 (C=O); 1391, 1367 (C-CH_3); 1150 (C-S);

δ_H (400 MHz; $CDCl_3$), 7.58 (2H, d, *J* 8.1 Hz Ar); 7.52 (2H, dt, *J* 8.3, 2.0 Hz, Ar); 7.47 (2H, tt, *J* 8.1, 2.0 Hz, Ar); 7.33 (1H, tt, *J* 7.3, 1.3 Hz, Ar); 7.26 (2H, dt, *J* 8.3, 2.0 Hz, Ar); 7.42- 7.32 (2H, m, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.92 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.23-3.14 (1H, m, C*H*); 3.05- 2.81 (4H, m, CH_2, CH_2); 1.22 (9H, s, C(CH_3)$_3$);

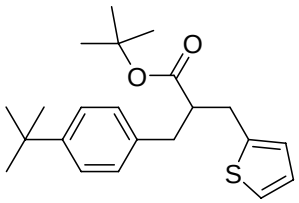
δ_C (75.5 MHz; $CDCl_3$); 173.7, 144.6, 141.6, 140.9, 139.2, 129.4, 128.7, 127.1, 127.0, 126.9, 126.6, 125.6, 123.7, 80.6, 50.2, 37.8, 32.2, 27.8;

MS (EI/CI) *m/z*; 378 (50% M-H^+);

HRMS (*CI*$^+$) *calcd* for $C_{24}H_{30}N_1O_2S_1$ [M+NH_4^+] *m/z* 396.1992 found: *m/z* 396.1994

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 11.44 (*R*) and 16.81 (*S*).

4.1.4.9: 3-(4-*tert*-Butyl-phenyl)-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.126)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-*tert*-butylphenylboronic acid (0.142 g, 0.80 mmol) were reacted under standard reaction conditions to generate the desired compound as a colourless oil (0.067 g, 93% yield);

R_f (petrol:dichloromethane, 2:1); 0.45

$[\alpha]_D^{20}$ = -5.1 º (*c*=1.1, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2996, 2869 (C-H); 1718 (C=O); 1391, 1265 (C-CH_3); 1153 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.30 (2H, d, *J* 8.3 Hz, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.13 (2H, d, *J* 8.3, Ar); 6.92 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.22-3.08 (1H, m, C*H*); 3.04- 2.94 (1H, m, CH_2); 2.93- 2.72 (3H, m, CH_2); 1.31 (9H, s, CH_3); 1.26 (9H, s, C(CH_3)$_3$).

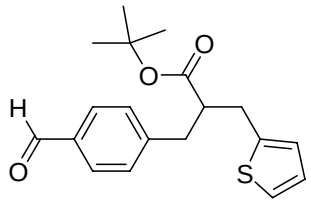
δ_C (75.5 MHz; $CDCl_3$); 173.8, 149.1, 141.8, 135.8, 128.7, 126.5, 125.5, 125.1, 123.5, 80.4, 50.2, 37.7, 34.3, 32.1, 31.3, 27.8;

MS (EI/CI) *m/z*; 359 (80% M-NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{22}H_{34}N_1O_2S_1$ [M+NH_4^+] *m/z* 359.2039 found: *m/z* 359.2043

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 6.47 (*R*) and 6.65 (*S*).

4.1.4.10: 3-(4-Formyl-phenyl)-2-thiophen-2-ylmethyl-propionic acid *tert*-butyl ester (2.127)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-formylphenylboronic acid (0.119 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.052 g, 79% yield);

R_f (petrol:dichloromethane, 2:1); 0.1;

$[\alpha]_D^{20}$ = -4.4 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2977, 2930 (C-H); 1698, 1720 (C=O); 1391, 1251 (C-CH_3); 1151 (C-S);

δ_H (300 MHz; $CDCl_3$), 10.0 (1H, s, C*H*O); 7.79 (2H, d, *J* 7.9 Hz, Ar); 7.34 (2H, d, *J* 7.9, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.92 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.22-3.08 (1H, m, C*H*); 3.04- 2.81 (4H, m, CH_2); 1.24 (9H, s, C(CH_3)$_3$);

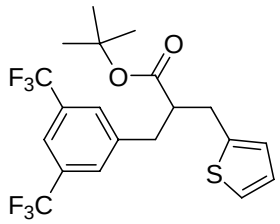
δ_C (75.5 MHz; $CDCl_3$); 191.9, 173.1, 146.4, 141.0, 134.7, 129.7, 129.6, 129.4, 126.6, 125.8, 123.9, 80.8, 53.3, 49.8, 38.1, 32.3, 27.7;

MS (EI/CI) *m/z*; 330 (45% M-H^+);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{26}N_1O_3S_1$ [M+NH_4^+] *m/z* 348.1628 found: *m/z* 348.1628.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 22.0 (*R*) and 24.3 (*S*).

4.1.4.11: 2-(3,5-Bis-trifluoromethyl-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.128)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 3,5-bis(trifluoromethyl) phenylboronic acid (0.13 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.076 g, 87% yield);

R_f (petrol:dichloromethane, 2:1); 0.45;

ν_{max} (neat)/cm^{-1}; 2981, 2934 (C-H); 1726 (C=O); 1153 (C-S); 1130, 1108 (C-F)

$[\alpha]_D^{20}$ = -4.1 º (*c*=0.95, $CHCl_3$);

δ_H (300 MHz; $CDCl_3$), 7.73 (1H, br s, p-Ph*H*), 7.48 (2H, br s, o-Ph*H*); 7.18 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.94 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.28- 3.15 (1H, m, C*H*); 3.09- 2.85 (4H, m, CH_2); 1.24 (9H, s, C(CH_3)$_3$);

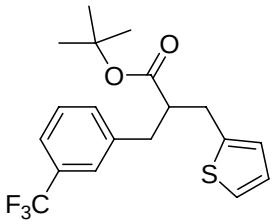
δ_C (75.5 MHz; $CDCl_3$); 172.8, 141.6, 140.5, 131.2 (q, *J* 193.1 Hz, 2x CF_3), 129.1 (q, *J* 1.24 Hz), 126.8, 126.0, 125.0, 124.1, 121.4, 120.4 (q, *J* 3.77 Hz), 120.4, 120.3, 81.3, 49.8, 37.4, 32.5, 27.6;

MS (EI/CI) *m/z*; (% M+NH_4^+); (%, MH^+); 264 ($C_{20}H_{20}F_6O_2S_1$+NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{20}H_{21}F_6O_2S_1$ [M+H^+] *m/z* 437.100995 found: *m/z* 437.1005.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 7.10 (*R*) and 7.60 (*S*).

4.1.4.12: 3-Thiophen-2-yl-2-(3-trifluoromethyl-benzyl)-propionic acid *tert*-butyl ester (2.129)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 3-trifluoromethylphenylboronic acid (0.152 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.074 g, 93% yield);

R_f (petrol:dichloromethane, 2:1); 0.4

$[\alpha]_D^{20}$ = -3.8 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2979, 2931 (C-H); 1724 (C=O); 1152 (C-S); 1125, 1074 (C-F).

δ_H (300 MHz; $CDCl_3$), 7.50-7.43 (2H, m, Ph); 7.37 (1H, br s, Ph); 7.16 (1H, dd, *J* 4.9, 1.1 Hz, C*H* thiophene); 6.92 (1H, dd, *J* 4.9, 3.4 Hz, C*H* thiophene); 6.83 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.24-3.15 (1H, m, C*H*); 3.04-2.84 (4H, m, CH_2, CH_2); 1.24 (9H, s, $C(CH_3)_3$);

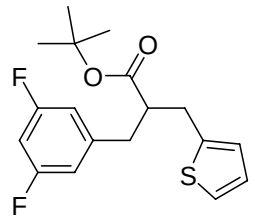
δ_C (75.5 MHz; $CDCl_3$); 173.2, 141.1, 139.9, 132.4, 128.6, 126.7, 125.8, 125.7, 125.6, 123.9, 123.2 (q, *J* 191.0 Hz, CF_3), , 80.8, 50.0, 37.8, 32.4, 27.7.

MS (EI/CI) *m/z*; 320 (60% $M+NH_4^+$); 371 (10%, MH^+); 332 (15% $C_{15}H_{13}O_2F_3S_1+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{25}O_2N_1F_3S_1$ [$M+NH_4^+$] *m/z* 388.1553 found: *m/z* 388.1553;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 5.82 (*R*) and 6.65 (*S*).

4.1.4.13: 2-(3,5-Difluoro-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.130)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 3,5-difluoro phenylboronic acid (0.126 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as colourless oils (0.067 g, 92% yield);

R_f (petrol:dichloromethane, 2:1); 0.45

$[\alpha]_D^{20}$ = -3.5 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2977, 2932 (C-H); 1725 (C=O); 1152 (C-S); 1118, 1040 (C-F).

δ_H (300 MHz; $CDCl_3$), 7.15 (1H, dd, *J* 4.9, 1.1 Hz, C*H* thiophene); 6.92 (1H, dd, *J* 4.9, 3.4 Hz, C*H* thiophene); 6.82 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 6.72 (1H, d, *J* 2.3 Hz, Ar); 6.70 (1H, d, *J* 2.3 Hz, Ar); 6.65 (1H, tt, *J* 9.0, 2.3 Hz, Ar); 3.22-3.12 (1H, m, C*H*); 3.02-2.74 (4H, m, CH_2, CH_2); 1.28 (9H, s, $C(CH_3)_3$).

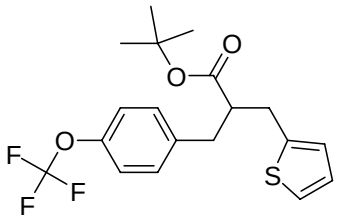
δ_C (75.5 MHz; $CDCl_3$); 173.1, 161.1 (d, *J* 260.5 Hz, C-F), 143.5, 143.3, 142.9 (t, *J* 9.30 Hz), 141.4, 127.1, 126.7, 125.8, 123.9, 111.9 (d, *J* 24.8 Hz), 101.8 (t, *J* 24.8 Hz), 80.9, 49.8, 37.6, 32.3, 27.8.

MS (EI/CI) *m/z*; 338 (65% $M+NH_4^+$); 339 (10%, MH^+); 300 (15% $C_{14}H_{16}O_2F_2S_1+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{18}H_{24}O_2N_1F_2S_1$ [$M+NH_4^+$] *m/z* 338.1152 found: *m/z* 338.1153;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, 8.40 (*R*) and 9.15 (*S*).

4.1.4.14: 3-Thiophen-2-yl-2-(4-trifluoromethoxy-benzyl)-propionic acid *tert*-butyl ester (2.131)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-trifluoromethoxy phenylboronic acid (0.164 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.056 g, 73% yield);

R_f (petrol:dichloromethane, 2:1); 0.35

$[\alpha]_D^{20}$ = -4.1 º (*c*=1.1, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2979. 2932 (C-H); 1725 (C=O); 1260, 1224 (C-F); 1154 (C-S).

δ_H (300 MHz; $CDCl_3$), 7.21 (2H, d, *J* 8.7 Hz, Ar); 7.17 (2H, d, *J* 8.7 Hz, Ar); 7.15 (1H, dd, *J* 4.9, 1.1 Hz, C*H* thiophene); 6.93 (1H, dd, *J* 4.9, 3.4 Hz, C*H* thiophene); 6.82 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.23-3.13 (1H, m, C*H*); 3.03-2.79 (4H, m, CH_2, CH_2); 1.24 (9H, s, $C(CH_3)_3$).

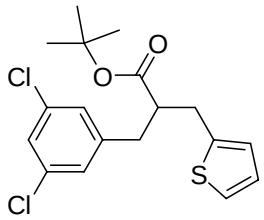
δ_C (75.5 MHz; $CDCl_3$); 173.4, 147.7, 141.2, 137.8, 130.3 (q, *J* 143.8 Hz CF_3), 126.6, 125.7, 123.8, 122.6, 122.1, 120.8, 118.7, 80.7, 50.2, 37.4, 32.3, 27.7.

MS (EI/CI) *m/z*; 404 (65% $M+NH_4^+$); 386 (5%, MH^+); 348 (20% $C_{15}H_{17}O_3F_3S_1+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{19}H_{25}O_3N_1F_3S_1$ [$M+NH_4^+$] *m/z* 404.1507 found: *m/z* 404.1507;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 9.02 (*R*) and 10.1 (*S*).

4.1.4.15: 2-(3,5-Dichloro-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.132)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 3,5-dichloro phenylboronic acid (0.151 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.059 g, 82% yield);

R_f (petrol:dichloromethane, 2:1); 0.30

$[\alpha]_D^{20}$ = -4.4 º (*c*=1.2, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2978, 2930 (C-H); 1725 (C=O); 1151 (C-S); 851, 798 (C-Cl).

δ_H (300 MHz; $CDCl_3$), 7.21 (1H, t, *J* 1.8 Hz, Ar); 7.15 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.07 (2H, d, *J* 1.8 Hz, Ar); 6.93 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.82 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.23-3.13 (1H, m, C*H*); 3.03-2.70 (4H, m, CH_2, CH_2); 1.29 (9H, s, $C(CH_3)_3$).

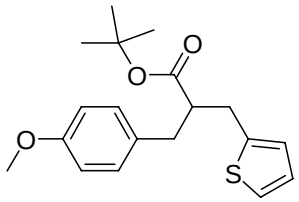
δ_C (75.5 MHz; $CDCl_3$); 173.0, 142.4, 140.8, 134.6, 127.5, 126.7, 126.5, 125.8, 123.9, 81.1, 49.8, 37.3, 32.3, 27.8.

MS (EI/CI) *m/z*; 371 (80% $M+H^+$); 332 (20% $C_{15}H_{17}O_3F_3S_1+NH_4^+$);

HRMS (*CI*$^+$) *calcd* for $C_{18}H_{21}O_2Cl_2S_1$ [$M+H^+$] *m/z* 371.0634 found: *m/z* 371.0634;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 7.98 (*R*) and 8.50 (*S*).

4.1.4.16: 2-(4-Methoxy-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.133)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-methoxy phenylboronic acid (0.121 g, 0.80 mmol) were reacted under the standard conditions to generate the desired compound as a colourless oil (0.055 g, 82% yield);

R_f (petrol:dichloromethane, 2:1); 0.2

$[\alpha]_D^{20}$ = -4.7 º (*c*=0.1.05, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2977, 2932 (C-H); 1724 (C=O); 1513 (CO-CH_3) 1367 (C-CH_3); 1150 (C-S). δ_H (400 MHz; $CDCl_3$), 7.20-7.13 (3H, m, Ar); 6.96 (1H, t, *J* 3.8 Hz, C*H* thiophene); 6.90-6.80 (3H, m, Ar); 3.84 (3H, s, OC*H*$_3$); 3.23-3.14 (1H, m, C*H*); 3.05- 2.76 (4H, m, C*H*$_2$); 1.33 (9H, s, C(C*H*$_3$)$_3$);

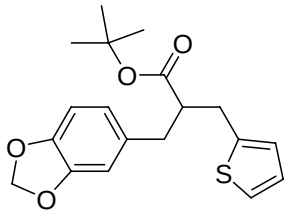
δ_C (75.5 MHz; $CDCl_3$); 191.9, 173.1, 146.4, 141.0, 134.7, 129.7, 129.6, 129.6, 126.6, 125.8, 123.9, 80.8, 53.3, 49.8, 38.1, 32.3, 27.7;

MS (EI/CI) *m/z*; 350 (65% M-NH_4^+);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{28}N_1O_3S_1$ [M+NH_4^+] *m/z* 350.1784 found: *m/z* 350.1781

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 9.57 (*R*) and 10.77 (*S*).

4.1.4.17: 2-Benzo[1,3]dioxol-5-ylmethyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.134)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and benzo[d][1,3]dioxol-5-ylboronic acid (0.132 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.047 g, 68% yield);

R_f (petrol:dichloromethane, 1:1); 0.2;

$[\alpha]_D^{20}$ = -4.0 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2978, 2930 (C-H); 1724 (C=O); 1248 (O-C-O) 1151 (C-S).

δ_H (300 MHz; $CDCl_3$), 7.13 (1H, dd, *J* 5.1, 1.1 Hz, C*H* thiophene); 6.90 (1H, dd, *J* 5.1, 3.4 Hz, C*H* thiophene); 6.81 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 6.71 (1H, t, *J* 7.9 Hz, Ar); 7.72 (1H, d, *J* 1.5 Hz, Ar); 6.63 (1H, dd, *J* 7.9, 1.5 Hz, Ar); 5.92 (2H, s, OCH_2O); 3.18-3.08 (1H, m, C*H*); 3.06-2.85 (4H, m, CH_2); 1.29 (9H, s, C(CH_3)$_3$);

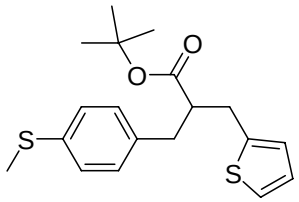
δ_C (75.5 MHz; $CDCl_3$); 173.6, 147.4, 145.9, 141.6, 132.6, 126.6, 125.5, 123.6, 122.0, 109.3, 108.0, 100.7, 80.5, 50.5, 37.9, 32.0, 27.8.

MS (EI/CI) *m/z*; 364 (30% M+NH_4^+); 347 (15%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{26}O_4N_1S_1$ [M+NH_4^+] *m/z* 364.1583 found: *m/z* 364.1580;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 14.1 (*R*) and 15.5 (*S*).

4.1.4.18: 2-(4-thiomethyl-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.135)



Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), 4-(methylthio)-phenylboronic acid (0.120 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless oil (0.056 g, 81% yield);

R_f (petrol:dichloromethane, 2:1; 0.2);

$[\alpha]_D^{20}$ = -4.7 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH_3); 1148 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.11 (2H, d, *J* 8.3 Hz, Ar); 7.06 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 7.03 (2H, d, *J* 8.3 Hz, Ar); 6.83 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.76 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.14-2.99 (1H, m, C*H*); 2.94-2.59 (4H, m, CH_2); 2.39 (3H, s, OSH_3); 1.20 (9H, s, C(CH_3)$_3$);

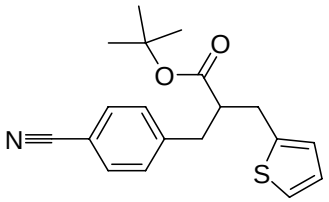
δ_C (75.5 MHz; $CDCl_3$); 174.0, 141.9, 136.4, 129.9 (2C), 127.3, 127.0, 126.0, 124.1, 81.0, 50.6, 38.0, 32.5, 28.2, 16.6.

MS (EI/CI) *m/z*; 348 (30% MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{19}H_{26}N_1O_2S_2$ [M+NH_4^+] *m/z* 366.5611 found: *m/z* 366.5614

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 10.35 (*S*) and 11.04 (*R*).

4.1.4.19: 2-(4-Cyano-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (2.136)



2-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol) and 4-cyano phenylboronic acid (0.117 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.041 g, 76% yield);

R_f (petrol:dichloromethane, 2:1); 0.1

$[\alpha]_D^{20}$ = -5.4 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2978, 2931 (C-H); 2228 (C≡N) 1724 (C=O); 1151 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.48 (2H, d, *J* 8.7 Hz, Ar); 7.21 (2H, d, *J* 8.7 Hz, Ar); 7.08 (1H, dd, *J* 5.3, 1.11 Hz, C*H* thiophene); 6.84 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.74 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.17-3.04 (1H, m, C*H*); 2.97-2.74 (4H, m, CH_2, CH_2); 1.17 (9H, s, $C(CH_3)_3$).

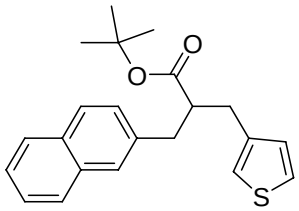
δ_C (75.5 MHz; $CDCl_3$); 172.9, 144.7, 140.7, 131.9 (2C), 129.7 (2C), 126.6, 125.8, 123.9, 118.8, 110.1, 80.9, 49.7, 37.9, 32.3, 27.7.

MS (EI/CI) *m/z*; 345 (80% $M+NH_4^+$); 328 (5% $M+H^+$); 289 (20% $C_{15}H_{17}N_2O_2S_1+NH_4^+$);

HRMS (CI^+) *calcd* for $C_{19}H_{25}N_2O_2S_1$ [$M+NH_4^+$] *m/z* 345.1637 found: *m/z* 345.1639;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 16.3 (*R*) and 17.3 (*S*).

4.1.4.20: 2-Naphthalen-2-ylmethyl-3-thiophen-3-yl-propionic acid *tert*-butyl ester (2.137)



3-Thiophen-2-ylmethyl-acrylic acid *tert*-butyl ester (0.045 g, 0.20 mmol), 2-naphthyl boronic acid (0.138 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as a colourless oil (0.057 g, 81% yield);

R_f (petrol:dichloromethane, 2:1) 0.35;

$[\alpha]_D^{20}$ = -3.3 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2929 (C-H); 1726 (C=O); 1148 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.81-7.65 (3H, m, Ar); 7.55 (1H, br s, Ar); 7.44-7.30 (2H, m, Ar); 7.24 (1H, dd, *J* 8.3, 1.5 Hz, Ar); 7.16 (1H, dd, *J* 4.9, 1.5 Hz, C*H* thiophene); 6.91 (1H, br s, C*H* thiophene); 6.86 (1H, dd, *J* 4.9, 1.2 Hz, C*H* thiophene); 3.14-2.67 (5H, m, CH_2, CH_2); 1.13 (9H, s, $C(CH_3)_3$);

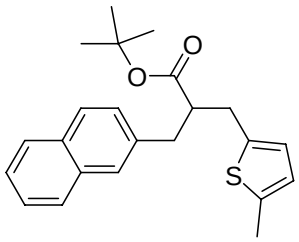
δ_C (75.5 MHz; $CDCl_3$); 174.1, 139.5, 136.7, 133.4, 132.1, 128.4, 127.8, 127.5, 127.4, 127.3, 125.9, 125.3, 125.2, 121.5, 80.3, 49.3, 38.6, 32.8, 27.8,

MS (EI/CI) *m/z*; 352 (10% MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{22}H_{24}O_2S_1$ [M+H^+] *m/z* 353.1570 found: *m/z* 353.1569

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 7.74 (*R*) and 8.47 (*S*).

5.1.4.21: 3-(3-Methyl-thiophen-2-yl)-2-naphthalen-2-ylmethyl-propionic acid *tert*-butyl ester (2.138)



2-(3-Methyl-thiophen-2-ylmethyl)-acrylic acid *tert*-butyl ester (0.048 g, 0.20 mmol), 2-naphthyl boronic acid (0.138 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as colourless oils (0.045 g, 62% yield);

$[\alpha]_D^{20}$ = -4.1 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH_3); 1148 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.84-7.74 (3H, m, Ar); 7.64 (1H, br s, Ar); 7.50-7.40 (2H, m, Ar); 7.34 (1H, dd, *J* 8.3, 1.9 Hz, Ar); 7.06 (1H, d, *J* 5.3 Hz, C*H* thiophene); 6.77 (1H, d, *J* 5.3 Hz, C*H* thiophene); 3.21-3.04 (2H, m, CH_2); 3.04-2.87 (3H, m, C*H*, CH_2); 2.13 (3H, s, CH_3); 1.23 (9H, s, C(CH_3)$_3$);

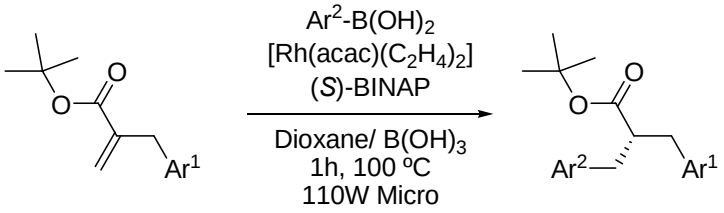
δ_C (75.5 MHz; $CDCl_3$); 173.9, 133.9, 133.4, 132.1, 129.7, 127.8, 127.5, 127.4, 127.4, 127.4, 125.9, 125.3, 121.8, 80.4, 50.1, 38.4, 30.3, 27.7, 13.7.

MS (EI/CI) *m/z*; 366 (30% MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{23}H_{27}O_2S_1$ [M+H^+] *m/z* 366.1654 found: *m/z* 366.1655

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 7.07 (*R*) and 7.43 (*S*).

4.1.5: General preparation of α- α substituted 3-Benzyl-2-Benzyl-2-ylmethyl-propionic acid *tert*-butyl esters



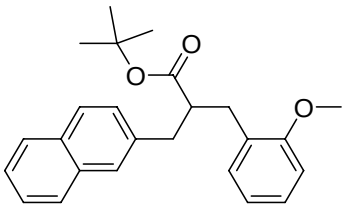
***via* heating methods (Method A):**

A 24 mL screw-capped vial equipped with a rubber septum was charged with *tert*-butyl 2-benzyl acrylate (0.045 g, 0.20 mmol), aryl boronic acid (0.098 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol). Dioxane (2 mL) and water (0.2 mL) were added *via* syringe under a stream of argon. The mixture was subsequently degassed for 5 minutes before being transferred with to a preheated hotplate at 100 °C for 20 h. The crude reaction mixture was diluted with diethyl ether (5 mL), filtered through a short plug of silica gel (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to give the title product.

***via* microwave irradiation (Method B):**

A 10 mL microwave tube equipped with a rubber septum was charged *tert*-butyl 2-benzyl acrylate (0.045 g, 0.20 mmol), aryl boronic acid (0.098 g, 0.80 mmol), acetylacetonatobis(ethylene)rhodium (I) (0.003 g, 0.008 mmol), (*S*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.007 g, 0.012 mmol) and boric acid (0.040 g, 0.80 mmol). Dioxane (2 mL) was added by syringe and the vessel was purged with argon for 5 minutes. The mixture was transferred to the microwave reactor (conditions; 110W, 100 ^{o}C) for 1 h. The crude reaction mixture was taken up in diethyl ether (5 mL), filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to yield the title product.

4.1.5.1: 3-(2-Methoxy-phenyl)-2-naphthalen-2-ylmethyl-propionic acid *tert*-butyl ester (2.139)



2-(2-Methoxy-benzyl)-acrylic acid *tert*-butyl ester (0.050 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.054 g, 71% yield);

R_f (petrol: ethyl acetate, 4:1); 0.4;

$[\alpha]_D^{20}$ = -6.4 º (*c*=1.05, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2973, 2933 (C-H); 1721 (C=O); 1510 (CO-CH_3) 1362 (C-CH_3);

δ_H (300 MHz; $CDCl_3$), 7.84-7.72 (3H, m, Ar), 7.65 (1, br s, naphthyl *H*); 7.48-7.38 (2H, m, Ar); 7.34 (1H, dd, *J* 8.3, 1.9 Hz, Ar); 7.23-7.11 (2H, m, Ar); 6.91-6.80 (2H, m, Ar); 3.80 (3H, s, O*CH*$_3$); .3.17-3.05 (2H, m, C*H,* C*H*$_2$); 2.99-2.83 (3H, m, C*H*$_2$); 1.16 (9H, s, C(C*H*$_3$)$_3$);

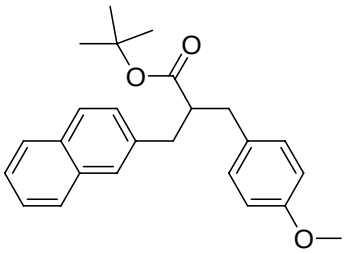
δ_C (75.5 MHz; $CDCl_3$); 174.5, 157.6, 137.2, 130.8, 127.5, 127.5, 127.5, 127.4, 127.2, 125.7, 125.1, 120.1, 110.0, 79.9, 55.1, 47.7, 38.7, 33.6, 28.0, 27.7;

MS (EI/CI) *m/z*; $C_{25}H_{32}NO_3$ (5% M+NH_4^+); $C_{25}H_{32}NO_3$ (5%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{25}H_{32}NO_3$ [M+NH_4^+] *m/z* 394.2377 found: *m/z* 394.2374.

HPLC Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 20.4 (*R*) and 24.1 (*S*).

4.1.5.2: 3-(4-Methoxy-phenyl)-2-naphthalen-2-ylmethyl-propionic acid *tert*-butyl ester (2.140)



Tert-butyl 2-(4-methoxybenzyl)acrylate (0.050 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.056 g, 74% yield);

R_f (petrol: ethyl acetate, 4:1); 0.4

$[\alpha]_D^{20}$ = -6.2 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2970, 2932 (C-H); 1722 (C=O); 1512 (CO-CH_3) 1360 (C-CH_3);

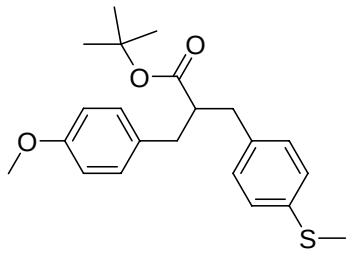
δ_H (300 MHz; $CDCl_3$), 7.84-7.72 (3H, m, Ar), 7.63 (1, br s, Ar); 7.49-7.39 (2H, m, Ar); 7.32 (1H, dd, *J* 8.3, 1.9 Hz, Ar); 7.12 (2H, d, *J* 8.9 Hz, Ar); 6.82 (2H, d, *J* 8.9 Hz, Ar); 3.79 (3H, s, O*CH*$_3$); 3.16-3.05 (1H, m, C*H,* C*H*$_2$); 2.99-2.86 (2H, m, C*H*$_2$); 2.84-2.70 (1H, m, C*H*$_2$); 1.19 (9H, s, C(C*H*$_3$)$_3$);

δ_C (75.5 MHz; $CDCl_3$); 174.3, 158.1, 137.0, 133.5, 132.2, 131.3, 130.0, 127.8, 127.6, 127.5, 127.5, 127.4, 125.9, 125.3, 113.7, 55.2, 50.3, 38.5, 37.7, 27.8.

HRMS (*CI*$^+$) *calcd* for $C_{25}H_{32}NO_3$ [M+NH_4^+] *m/z* 394.2377 found: *m/z* 394.2373.

HPLC Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 13.5 (*R*) and 14.8 (*S*).

4.1.5.3: 3-(4-Methoxy-phenyl)-2-(4-methylsulfanyl-benzyl)-propionic acid *tert*-butyl ester (2.141)



Tert-butyl 2-(4-methoxybenzyl)acrylate (0.050 g, 0.20 mmol) and 4-thiomethylphenyl boronic acid (0.134 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.052 g, 70% yield);

R_f (petrol: ethyl acetate, 4:1); 0.2

$[\alpha]_D^{20}$ = -5.9 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2976, 2922 (C-H); 1724 (C=O); 1512 (CO-CH_3); 1148 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.17 (2H, d, *J* 8.3 Hz, Ar); 7.10 (2H, d, *J* 1.9 Hz, Ar); 7.07 (2H, d, *J* 1.9 Hz, Ar); 6.80 (2H, d, *J* 8.3 Hz, Ar); 3.78 (3H, s, O*CH*$_3$); 2.91-2.78 (3H, m, C*H,* C*H*$_2$); 2.75-2.66 (2H, m, C*H,* C*H*$_2$); 2.46 (3H, s, OS*H*$_3$); 1.22 (9H, s, C(C*H*$_3$)$_3$);

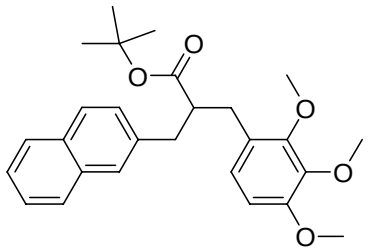
δ_C (75.5 MHz; $CDCl_3$); 174.1, 158.1, 136.5, 135.8, 131.2 (2C), 129.9, 129.5 (2C), 126.9 (2C), 113.6, 55.2, 50.2, 27.8, 16.2;

MS (EI/CI) *m/z*; $C_{22}H_{32}NO_3S_1$ (45% $M+NH_4^+$); $C_{22}H_{28}O_3S_1$ (50%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{22}H_{32}NO_3S_1$ [$M+NH_4^+$] *m/z* 373.1832 found: *m/z* 373.1828.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 11.7 (*R*) and 13.4 (*S*).

4.1.5.4: 3-Naphthalen-2-yl-2-(2,3,4-trimethoxy-benzyl)-propionic acid *tert*-butyl ester (2.142)



Tert-butyl 2-(2,3,4-trimethoxybenzyl)acrylate (0.062 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.051 g, 58% yield);

R_f (petrol: ethyl acetate, 4:1); 0.1

ν_{max} (neat)/cm^{-1}; 2976, 2922 (C-H); 1724 (C=O); 1627, 1618 (O-CH_3);.

δ_H (300 MHz; $CDCl_3$), 7.82-7.73 (3H, m, Ar), 7.65 (1H, br s, Ar); 7.49-7.38 (2H, m, Ar); 7.34 (1H, dd, *J* 8.7, 1.9 Hz, Ar); 6.75 (1H, d, *J* 8.3 Hz, Ar); 6.48 (1H, d, *J* 8.3 Hz, Ar); 3.77 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 3.74 (3H, s, OCH_3); 3.09-2.90 (2H, m, CH_2); 2.90-2.67 (3H, m, C*H,* CH_2); 1.20 (9H, s, C(CH_3)$_3$);

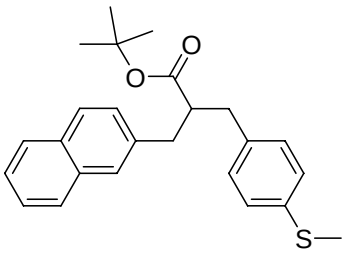
δ_C (75.5 MHz; $CDCl_3$); 174.5, 152.4, 152.1, 142.1, 137.1, 133.4, 132.1, 127.7, 127.5, 127.5, 127.4, 127.2, 125.8, 125.1, 124.8, 106.7, 60.7, 60.6, 48.6, 38.7, 33.2, 27.8.

MS (EI/CI) *m/z*; 454 (20% M+NH_4^+); 436 (10%, MH^+); 398 (50% $C_{23}H_{28}NO_5$);

HRMS (*CI*$^+$) *calcd* for $C_{27}H_{36}N_1O_5$ [M+NH_4^+] *m/z* 454.2593 found: *m/z* 454.2594.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 12.2 (*R*) and 16.6 (*S*).

4.1.5.5: 2-(4-Methylsulfanyl-benzyl)-3-naphthalen-2-yl-propionic acid *tert*-butyl ester (2.143)



2-(4-Methylsulfanyl-benzyl)-acrylic acid *tert*-butyl ester (0.054 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as a yellow oil (0.061 g, 78% yield);

R_f (petrol: ethyl acetate, 4:1); 0.5

$[\alpha]_D^{20}$ = -5.4 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2980, 2978 (C-H); 1726 (C=O); 1473 (S-CH_3).

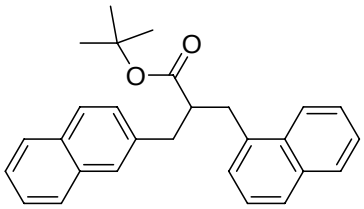
δ_H (300 MHz; $CDCl_3$), 7.85-7.72 (3H, m, Ar), 7.63 (1H, br s, Ar); 7.50-7.39 (2H, m, Ar); 7.33 (1H, dd, *J* 8.3, 1.9 Hz, Ar); 7.20 (2H, d, *J* 8.7 Hz, Ar); 7.13 (2H, d, *J* 8.7 Hz, Ar); 3.04-3.17 (1H, m, C*H,* CH_2); 3.02-2.89 (3H, m, CH_2); 2.85-2.73 (1H, m, CH_2); 2.47 (3H, s, SCH_3); 1.20 (9H, s, C(CH_3)$_3$);

δ_C (75.5 MHz; $CDCl_3$); 174.0, 141.5, 136.7, 136.3, 135.8, 133.4, 132.1, 129.5, 129.4, 127.8, 127.5, 127.4, 127.3, 126.8, 125.8, 125.2, 125.1, 80.3, 49.9, 38.5, 37.9, 27.9, 27.7, 16.1.

MS (EI/CI) *m/z*; 410 (50% M+NH_4^+); 392 (10%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{25}H_{32}N_1O_2S_1$ [M+NH_4^+] *m/z* 410.2154 found: *m/z* 410.2157.

4.1.5.6: 3-Naphthalen-2-yl-2-naphthalen-1-ylmethyl-propionic acid *tert*-butyl ester (2.144)



Tert-butyl 2-(naphthalen-1-ylmethyl)acrylate (0.050 g, 0.20 mmol) and), 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.068 g, 86% yield);

R_f (petrol: ethyl acetate, 9:1); 0.4

$[\alpha]_D^{20}$ = -7.1 º (*c*=1.2, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2977 (C-H); 1723 (C=O); 1149 (OC-CH_3);

δ_H (400 MHz; $CDCl_3$), 7.91-7.70 (6H, m, Ar), 7.67 (1, br s, naphthyl); 7.50-7.40 (4H, m, Ar); 7.38 (2H, d, *J* 4.6 Hz, Ar); 7.34 (1H, dd, *J* 8.5, 1.6 Hz, Ar); 3.49-3.40 (1H, m, C*H,* CH_2); 3.34-3.13 (3H, m, C*H,* CH_2); 3.05-2.97 (1H, m, CH_2); 1.15 (9H, s, C(CH_3)$_3$);

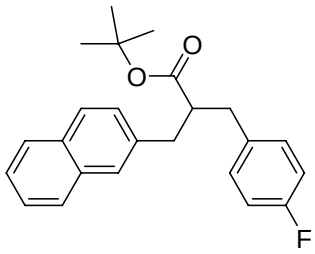
δ_C (75.5 MHz; $CDCl_3$); 174.2, 136.8, 135.3, 133.8, 132.2, 131.8, 128.7, 127.8, 127.5, 127.5, 127.4, 127.2, 127.1, 125.9, 125.8, 125.4, 125.3, 125.2, 123.6, 80.3, 49.2, 38.9, 35.4, 27.7;

MS (EI/CI) *m/z*; $C_{28}H_{32}NO_2$ (80% M+NH_4^+); $C_{28}H_{28}O_2$ (15%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{25}H_{32}NO_3$ [M+NH_4^+] *m/z* 414.2428 found: *m/z* 414.2429.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 13.9 (*R*) and 15.6 (*S*).

4.1.5.7: 2-(4-Fluoro-benzyl)-3-naphthalen-2-yl-propionic acid *tert*-butyl ester (2.145)



Tert-butyl 2-(4-fluorobenzyl)acrylate (0.047 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.061 g, 83% yield);

R_f (petrol: ethyl acetate, 9:1); 0.4

$[\alpha]_D^{20}$ = -5.7 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2977, 2930 (C-H); 1723 (C=O); 1148 (C-F);

δ_H (300 MHz; $CDCl_3$), 7.84-7.72 (3H, m, Ar), 7.65 (1, br s, Ar); 7.50-7.38 (2H, m, Ar); 7.33 (1H, dd, *J* 8.3, 1.8 Hz, Ar); 7.20-7.11 (2H, m, Ar); 6.95 (2H, tt, *J* 8.7, 2.3 Hz, Ar); 3.18-3.03 (1H, m, C*H,* CH_2); 3.11-2.72 (4H, m, CH_2); 1.17 (9H, s, C(CH_3)$_3$);

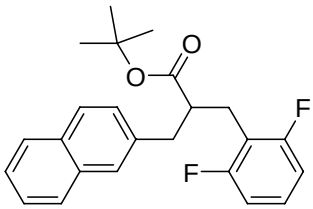
δ_C (75.5 MHz; $CDCl_3$); 174.0, 136.6, 134.9, 134.9, 133.4, 132.1, 130.4, 130.3, 127.8, 127.5, 127.4, 127.4, 127.3, 125.9, 125.3, 115.1, 114.8, 80.4, 50.1, 50.1, 38.6, 37.6, 27.7;

MS (EI/CI) *m/z*; $C_{24}H_{29}NF_1O_2$ (60% $M+NH_4^+$); $C_{24}H_{29}NF_1O_2$ (25%, MH^+);

HRMS (*CI*$^+$) *calcd* for $C_{24}H_{29}NF_1O_2$ [$M+NH_4^+$] *m/z* 382.2177 found: *m/z* 382.2179.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 10.98 (*R*) and 11.69 (*S*).

4.1.5.8: 2-(2,6-Difluoro-benzyl)-3-naphthalen-2-yl-propionic acid *tert*-butyl ester (2.146)



2-(2,6-Difluoro-benzyl)-acrylic acid *tert*-butyl ester (0.051 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.052 g, 79% yield);

R_f (petrol: ethyl acetate, 9:1); 0.5

$[\alpha]_D^{20}$ = -5.7 º (*c*=1.2, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2973, 2932 (C-H); 1725 (C=O); 1150, 734 (C-F).

δ_H (300 MHz; $CDCl_3$), 7.82-7.73 (3H, m, Ar), 7.65 (1H, br s, Ar); 7.49-7.38 (2H, m, Ar); 7.34 (1H, dd, *J* 8.7, 1.9 Hz, Ar); 7.24-7.14 (1H, m, Ar); 6.97 (2H, t, *J* 7.6 Hz, Ar); 3.25-3.00 (3H, m, C*H,* CH_2); 3.0-2.52 (2H, m, CH_2); 1.19 (9H, s, C(CH_3)$_3$);

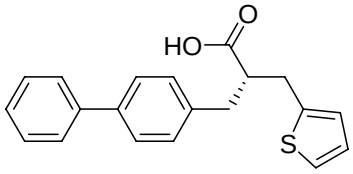
δ_C (75.5 MHz; $CDCl_3$); 173.4, 163.3, 163.2, 160.0, 159.9, 136.6, 133.4, 132.1, 128.1, 127.9, 127.8, 127.5, 127.4, 127.4, 127.3, 125.8, 125.2, 115.0, 111.1, 110.9, 110.8, 80.4, 47.5, 47.4, 38.5, 28.0, 27.6, 25.4, 25.4.

MS (EI/CI) *m/z*; 400 (25% M+NH_4^+); 383 (5%, MH^+); 344 (45% $C_{20}H_{20}F_2NO_2$);

HRMS (*CI*$^+$) *calcd* for $C_{24}H_{28}N_1F_2O_2$ [M+NH_4^+] *m/z* 400.2083 found: *m/z* 400.2084.

Diacel Chiralcel AD, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 7.14 (*R*) and 8.26 (*S*).

4.1.5.9: (*S*)-3-Biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid (2.147)



A 10 mL round bottom flask was charged with (*S*)-2-Biphenyl-4-ylmethyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (0.150 g, 0.40 mmol) in dichloromethane (5 mL). To this was added trifluoroacetic acid (0.5 mL) and the reaction stirred at room temperature for 6 hours. Upon completion the crude reaction mixture was concentrated *in vacuo* and azeotroped with dichloromethane (3 x 5 mL). Recrystallisation from petrol-diethyl ether gives the title product as a white solid (0.125 g, 97% yield).

R_f (petrol: ethyl acetate, 1:2); 0.1

$[\alpha]_D^{20}$ = -12.6 º (*c*=1.0, CH_3OH);

mp (EtOH) 158-160 ºC;

ν_{max} (KBr)/cm^{-1}; 3029 (O-H); 2976, 2930, (C-H); 1724 (C=O); 1150 (C-S);

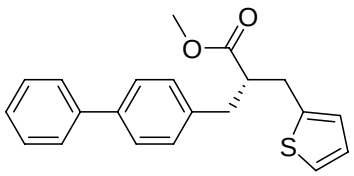
δ_H (250 MHz; CDCl3), 11.2 (1H, br s, COO*H*); 7.57-7.40 (4H, m, Ar); 7.40 (2H, tt, *J* 8.1, 2.0 Hz, Ar); 7.23 (1H, tt, *J* 7.3, 1.3 Hz, Ar); 7.21-7.00 (2H, m, Ar); 7.12 (1H, dd, *J* 5.3, 1.1 Hz, C*H* thiophene); 6.08 (1H, dd, *J* 5.3, 3.4 Hz, C*H* thiophene); 6.79 (1H, dd, *J* 3.4, 0.75 Hz, C*H* thiophene); 3.23-3.14 (1H, m, C*H*); 3.05- 2.81 (4H, m, CH_2);

δ_C (75.5 MHz; CDCl3); 166.8, 141.0, 140.7, 139.4, 137.5, 129.3, 128.7, 127.2, 127.1, 126.9, 126.8, 125.8, 123.9, 64.3, 49.4, 37.0, 31.5;

MS (EI) *m/z*; 322 (15%, M^+);

HRMS (CI^+) *calcd* for $C_{20}H_{18}O_2S_1$ [M +] *m/z* 322.1022 found: *m/z* 322.1025.

4.1.5.10: (*S*)-3-Biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid methyl ester (2.148)



(*S*)-3-Biphenyl-4-yl-2-thiophen-2-ylmethyl-propionic acid (0.05 g, 0.15 mmol) and potassium carbonate (0.09 g, 0.60 mmol) were added to a 25 mL tube capped with rubber septum in anhydrous acetonitrile (3 mL). Methyl iodide (0.04 g, 0.30 mmol) was added and the suspension stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo*, and extracted with dichloromethane (5 mL) and washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated to generate the desired compound as a white solid (0.049 g, 97% yield)

R_f (petrol:dichloromethane, 2:1); 0.5

Mp (EtOH) = 60-63 ºC

$[\alpha]_D^{20}$ = -6.6 º (*c*=1.0, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 3029, 2950 (C-H); 1736 (C=O); 1164 (C-S);

δ_H (300 MHz; $CDCl_3$), 7.49 (2H, dd, *J* 8.3, 1.5 Hz Ar); 7.43 (2H, d, *J* 8.3 Hz, Ar); 7.34 (2H, tt, *J* 7.9 Hz, Ar); 7.24 (1H, tt, *J* 7.2, 1.5 Hz, Ar); 7.15 (2H, d, *J* 8.3 Hz, Ar); 7.06 (1H, dd, *J* 4.9, 1.1 Hz, C*H* thiophene); 6.83 (1H, dd, *J* 4.9, 3.4 Hz, C*H* thiophene); 6.73 (1H, dd, *J* 3.4, 1.1 Hz, C*H* thiophene); 3.50 (3H, s, OCH_3); 3.19-3.07 (1H, m, C*H*); 3.03- 2.89 (2H, m, CH_2, C*H*); 2.86-2.73 (1H, m, C*H*).

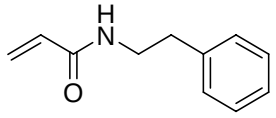
δ_C (75.5 MHz; $CDCl_3$); 174.8, 141.2, 140.8, 139.3, 137.7, 129.2, 128.7, 127.1, 126.9, 126.7, 125.6, 123.9, 51.6, 49.6, 37.4, 31.8.

HRMS (ESI^+) *calcd* for $C_{21}H_{20}O_2S_1$ [$M+H^+$] *m/z* 359.1082 found: *m/z* 359.1073;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1}, t_R = 15.2 (*R*) and 17.6 (*S*).

4.1.6: Natural Product Materials

4.1.6.1: *N*-Phenethyl-acrylamide (3.71)



Phenethylamine (2.42 g, 20 mmol) was charged to a 50 mL round bottomed flask and dissolved in anhydrous dichloromethane (25 mL). The resulting solution was cooled to 0 ºC (ice/water). To the cooled flask was added anhydrous triethylamine (2.12 g, 21 mmol) followed by dropwise addition of acryloyl chloride (1.90 g, 21 mmol in 5 mL dichloromethane) with vigorous stirring. The mixture was stirred for a further 3 hours at 4 ºC. Upon warming to room temperature reaction was quenched with 1M HCl solution (30 mL) and the organic phase extracted, washed with 1M NaOH (30 mL) then brine (30 mL), dried ($NaSO_4$) and concentrated to give orange oils. The crude mixture was eluted through a short pad of silica gel (6:1 Petrol:EtOAc) gave the title product as a light yellow oil. (Yield 3.26 g, 93%)

R_f (petrol: ethyl acetate, 3:1) 0.15;

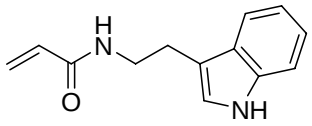
ν_{max} (neat)/cm^{-1}; 3279 (N-H), 3028,1657 (C=O), 1625, 985, 958 (C=CH_2);

δ_H (300 MHz; $CDCl_3$), 7.22-7.10 (5H, m, Ph); 6.16 (1H, dd, *J* 17.0, 1.5 Hz, C*H*CH_2); 6.0 (1H, dd, *J* 17.0, 10.0 Hz, CHC*H*$_2$); 5.52 (1H, br s, N*H*); 5.52 (1H, dd, *J* 10.2, 1.1 Hz, CHC*H*$_2$); 3.49 (2H, q, *J* 7.2 Hz, C*H*$_2$); 0.87 (3H, t, *J* 6.8 Hz, C*H*$_2$).

δ_C (75.5 MHz; $CDCl_3$); 138.7, 165.5, 130.8, 128.6, 128.5, 126.4, 126.1, 40.6, 35.4.

All data in correspondence with literature values [7]

4.1.6.2: *N*-[2-(1*H*-Indol-3-yl)-ethyl]-acrylamide (3.72)



Tryptamine (2.40 g, 15 mmol) was charged to a 100 mL round bottomed flask and dissolved in anhydrous dichloromethane (40 mL). The resulting solution was cooled to 0 ºC (ice/water). To the cooled flask anhydrous triethylamine (1.62 g, 16 mmol) was added followed by dropwise addition of acryloyl chloride (1.44 g, 16 mmol in 5 mL dichloromethane) with vigorous stirring. The mixture was stirred for a further 3 hours at 4 ºC. Upon warming to room temperature reaction was quenched with 1M HCl solution (50 mL) and the organic phase extracted, washed with 1M NaOH (50 mL) then brine (50 mL), dried ($NaSO_4$) and concentrated to give orange oils. The crude mixture was eluted through a short pad of silica gel (2:1 Petrol:EtOAc) gave the title product as a yellow oil. (Yield 2.06 g, 64%)

R_f (petrol: ethyl acetate, 1:1) 0.1;

ν_{max} (neat)/cm^{-1}; 3439 3309 (N-H), 3022,1667 (C=O), 1628, 976, 911 (C=CH_2);

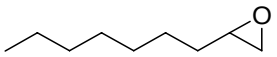
δ_H (300 MHz; $CDCl_3$), 8.20 (1H, br s, N*H* indole); 7.61 (1H, d, *J* 7.9 Hz, C*H* indole); 7.38 (1H, d, *J* 7.9 Hz, C*H* indole); 7.22 (1H, t, *J* 7.9 Hz, C*H* indole); 7.13 (1H, t, *J* 7.9 Hz, C*H* indole); 7.03 (1H, s, C*H* indole); 6.25 (1H, dd, *J* 17.0, 1.5 Hz, C*H*CH_2); 6.0 (1H, dd, *J* 17.0, 10.0 Hz, CHC*H*$_2$); 5.68 (1H, br s, N*H*); 5.60 (1H, dd, *J* 10.0, 1.5 Hz, CHC*H*$_2$); 3.69 (2H, q, *J* 6.8, C*H*$_2$); 3.02 (2H, t, *J* 6.8 Hz, C*H*$_2$);

δ_C (75.5 MHz; $CDCl_3$); 165.5, 136.4, 130.9, 127.3, 126.2, 122.2, 122.0, 119.5, 118.6, 112.8, 111.2, 39.7, 25.2.

HRMS (ESI$^-$) *calcd* for $C_{13}H_{14}N_2O_1$ [M+H^+] *m/z* 213.1028 found: *m/z* 213.1036;

All data in correspondence with literature values [8]

4.1.6.3: 2-Heptyloxirane (3.18)



1-Nonene (25.0 g, 0.20 mol) was charged to a 500 mL 3-necked round bottomed flask equipped with nitrogen inlet and pressure equalising dropping funnel, and dissolved in anhydrous dichloromethane (150 mL). The resulting solution was cooled to 0 ºC (ice/water). The dropping funnel was charged with a filtered solution of 75% meta-chloroperoxybenzoic acid (62.0 g, 3.5 mol) in dichloromethane (200 mL). The solution was added dropwise over 45 minutes at 4 ºC. The mixture was stirred for a further 3 hours at 4 ºC and 1h at room temperature. The reaction was quenched with 10% potassium thiosulfate (300 mL) and extracted with saturated sodium bicarbonate solution (2x 250 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated to give crude product. The epoxide was distilled under high vacuum (55 ºC, 5 mmHg) to give the title product as colourless oils. (Yield 23.7 g, 84%)

R_f (petrol: ethyl acetate, 20:1) 0.6;

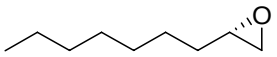
ν_{max} (neat)/cm^{-1}; 2958, 2930, 2858 (C-H), 916, 838 (C-O epoxide);

δ_H (300 MHz; $CDCl_3$), 2.90-2.80 (1H, m, C*H*OCH_2); 2.68 (1H, dd, *J* 4.9, 4.1 Hz, CHOC*H*$_2$); 2.4 (1H, dd, *J* 4.9, 3.0 Hz, CHOC*H*$_2$); 1.60-1.19 (12H, m, C*H*$_2$); 0.83 (3H, t, *J* 6.6 Hz, C*H*$_3$);

δ_C (75.5 MHz; $CDCl_3$); 52.1, 46.8, 32.3, 31.6, 29.2, 29.0, 25.8, 22.4, 13.8,

All data in correspondence with literature values [9]

4.1.6.4: (*S*)-(-)-Heptyloxirane [(*S*)-3.18]



(*S,S*)-*N*,*N*'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (0.30 g, 0.50 mmol) was charged to a 25 mL round bottomed flask. Dichloromethane (2 mL) and acetic acid (300 μL) were added and the red solution stirred in air for 30 minutes. The resulting brown solution was concentrated in *vacuo* to give a brown residue. The active catalyst was dissolved in neat 2-heptyloxirane (14.2 g, 100 mmol) with anhydrous THF (2 mL) and the flask cooled to 0 ºC (ice/water). Water (1.0 mL, 55 mmol, 0.55 eq) was added dropwise. The mixture was capped with a greased glass stopper and stirred for 48 hours at 23 ºC. After this time the reaction flask was attached to a short path distillation head and the volatiles distilled under high vacuum (55 ºC, 5 mmHg). The recovered epoxide was passed through a short silica pad to removed residual water and THF to give the title product as a colourless oil (Yield 6.12 g, 43%, 86% theoretical maximum)

R_f (petrol:ethyl acetate, 20:1) 0.6;

$[\alpha]_D^{20}$ = -8.7º (*c*=1.15, $CHCl_3$);

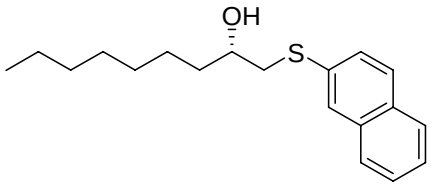
ν_{max} (neat)/cm^{-1}; 2958, 2930, 2858 (C-H), 916, 838 (C-O epoxide);

δ_H (300 MHz; $CDCl_3$), 2.90-2.80 (1H, m, C*H*OCH_2); 2.68 (1H, dd, *J* 4.9, 4.1 Hz, CHOCH_2); 2.4 (1H, dd, *J* 4.9, 3.0 Hz, CHOCH_2); 1.60-1.19 (12H, m, CH_2); 0.83 (3H, t, *J* 6.6 Hz, CH_3);

δ_C (75.5 MHz; $CDCl_3$); 52.1, 46.8, 32.3, 31.6, 29.2, 29.0, 25.8, 22.4, 13.8,

All data in correspondence with literature values [9]

4.1.6.5: (*S*)-1-(naphthalen-2-ylthio)nonan-2-ol (3.80)



2-Naphthene thiol (0.336 g, 2.1 mmol) was charged to a 25 mL round bottomed flask and dissolved in anhydrous methanol (10 mL). The resulting solution was cooled to 0 ºC (ice/water). To the cooled flask, anhydrous triethylamine (0.253 g, 2.5 mmol) was added followed by (S)-2-heptyloxirane (0.280 g, 2.0 mmol) with vigorous stirring. The mixture was stirred for a further 16 hours at 4 ºC. Upon warming to room temperature silica was added (0.50 g) and the mixture was concentrated. Elution by column chromatography (40:1-20:1 gradient petrol: diethyl ether) gave the title product as a white solid. (Yield 0.206 g, 34%)

R_f (petrol:ethyl acetate, 40:1) 0.10;

mp (hexane) 65-67 °C;

$[\alpha]_D^{20}$ = -27º (*c*=1.50, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}; 3426 (O-H), 2927 (C-H); 2856 (C-S-Ar);

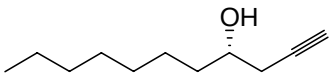
δ_H (300 MHz; $CDCl_3$), 7.86-7.70 (4H, m, naphthalene); 7.54-7.41 (3H, m, naphthalene); 3.78-3.66 (1H, m, C*H*OH); 3.26 (1H, dd, *J* 14.0, 3.9 Hz, C*H*S); 2.94 (1H, dd, *J* 14.0, 8.7 Hz, C*H*S); 2.34 (1H, br s, O*H*); 1.63-1.39 (3H, m, CH_2), 1.39-1.17 (10H, m, CH_2); 0.87 (3H, t, *J* 6.8 Hz, CH_3);

δ_C (75.5 MHz; $CDCl_3$); 134.1, 133.2, 132.4, 128.6, 128.1, 127.8, 127.6, 127.1, 126.6, 125.9, 69.4, 42.1, 36.1, 31.7, 29.5, 29.1, 25.6, 22.6, 14.0

HRMS (ESI^+) *calcd* for $C_{19}H_{26}O_1S_1Na_1$ [$M+Na^+$] *m/z* 325.1602 found: *m/z* 325.1594;

Diacel Chiralcel OD-H, hexane/propan-2-ol (99.9:0.01), 1 mL min^{-1}, t_R = 37.95 (*S*) and 53.3 (*R*). 96% ee.

4.1.6.6: (S)-Undec-1-yn-4-ol (3.16)



Lithium acetylide EDA complex (8.38 g, 91 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous dimethysulfoxide (45 mL). The resulting reaction mixture was immersed in a room temperature water bath. To the brown-black suspension was added (*S*)-2-heptyloxirane (4.98 g, 35.0 mmol) in one portion with vigorous stirring. The mixture was stirred for a further 2 hours at 23 ºC. Upon completion the suspension was poured into 4 ºC water (150 mL) and stirred for 30 minutes to quench excess acetylide. This was then filtered through a pad of Celite® washing with diethyl ether (3 x 100 mL). The combined washings were then extracted with water (2 x 100 mL), brine (2 x 150 mL), dried ($NaSO_4$) and concentrated. Final traces of DMSO and water were removed through a short silica pad to give the title product as golden yellow oils (yield 5.420 g, 92%)

R_f (petrol:ethyl acetate, 9:1) 0.2;

$[\alpha]_D^{20}$ = -23.0º (*c*=1.23, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}; 3401 (O-H), 3300 (C-H alkyne); 2856 (C≡C);

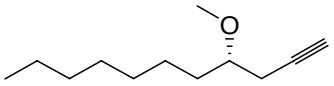
δ_H (300 MHz; $CDCl_3$), 3.69 (1H, quint, *J* = 5.5, C*H*OH); 2.31 (2H, ddd, *J* 17.0, 5.5, 2.6 Hz, CHOCH_2); 1.99 (1H, t, *J* 2.6 Hz, CH_2CC*H*); 1.58-1.64 (13H, m, CH_2); 0.81 (3H, t, *J* 6.6 Hz, CH_3);

δ_C (75.5 MHz; $CDCl_3$); 80.9, 70.6, 69.8, 36.1, 31.7, 29.4, 29.1, 27.2, 25.5, 22.5, 14.0.

HRMS (ESI^+) *calcd* for $C_{11}H_{19}O_1Na_1$ [M+Na^+] *m/z* 190.2577 found: *m/z* 190.2583;

All data in correspondence with literature values [10]

4.1.6.7: (*S*)-4-Methoxy-undec-1-yne (3.12)



A 60% sodium hydride suspension in mineral oil (1.06 g, 44.1 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous tetrahydrofuran (80 mL). The resulting mixture was cooled to 0 ºC (ice/water) and to this was added (S)-undec-1-yn-4-ol (5.05 g, 30.0 mmol) in one portion, followed by methyl iodide (5.12 g, 36 mmol). The mixture was allowed to warm to room temperature over 1 hour and then refluxed for a further 16 hours. Upon completion the suspension was concentrated in *vacuo,* and then resuspended in diethyl ether (100 mL). The organic phase was extracted with water (2 x 100 mL), brine (2 x 150 mL), dried ($MgSO_4$) and concentrated. Product was isolated by column chromatography (40:1 petrol: diethyl ether) to give the title compound as colourless oils (yield 5.360 g, 98%)

R_f (petrol: ethyl acetate, 20:1) 0.7;

$[\alpha]_D^{20}$ = -33º (*c*=1.2, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 3306 (C-H Alkyne); 2929 (C-O); 2857 (C≡C)

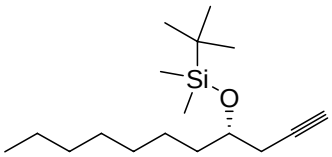
δ_H (300 MHz; $CDCl_3$), 3.37 (3H, s, OCH_3); 3.29 (1H, quint, *J* 5.7 Hz, $CHOCH_3$), 2.27 (2H, ddd, *J* 17.0, 5.3, 2.6 Hz, $CHCH_2CCH$); 1.97 (1H, t, *J* 2.6 Hz, $CHCH_2CCH$); 1.66-1.49 (2H, m, CH_2); 1.48-1.19 (10H, m, CH_2); 0.87 (3H, t, *J* 6.60 Hz, CH_3);

δ_C (75.5 MHz; $CDCl_3$); 81.1, 79.2, 69.7, 56.9, 33.5, 31.7, 29.2, 25.1, 23.0, 22.5, 14.0.

HRMS (ESI^+) *calcd* for $C_{12}H_{22}NaO$ [$M+Na^+$] *m/z* 182.3025 found: *m/z* 182.3021;

All data in correspondence with literature values [10]

4.1.6.8: *tert*-Butyl-dimethyl-((S)-1-prop-2-ynyl-octyloxy)-silane (3.82)



(*S*)-undec-1-yn-4-ol (2.51 g, 15.0 mmol) was charged to a 100 mL round bottomed flask and dissolved in anhydrous dimethylformamide (60 mL). To the resulting solution was added sequentially *tert*-butylchlorodimethylsilane (2.71 g, 18.0 mmol) followed by imidazole (3.06 g, 45 mmol) the mixture was then heated at 65 ºC for 16 hours. Upon completion the solution was poured into 4 ºC water (150 mL) and stirred for 30 minutes. The organic phase was extracted with water (2 x 100 mL), brine (2 x 100 mL), dried ($MgSO_4$) and concentrated. The material was isolated by column chromatography (40:1 petrol: diethyl ether) to give the title product as light yellow oils (yield 3.98 g, 94%)

R_f (petrol: diethyl ether, 40:1; 0.6);

$[\alpha]_D^{20}$ = -23º (*c*=1.05, $CHCl_3$);

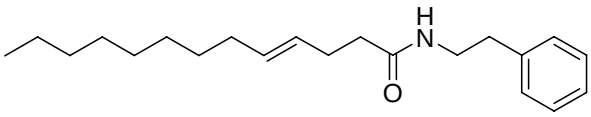
ν_{max} (neat)/cm^{-1}; 3309 (C-H alkyne); 2955, 2930, (C-O); 2858 (C≡C); 1098, 837.1 (O-Si)

δ_H (300 MHz; $CDCl_3$), 3.71 (1H, quint, *J* 5.7 Hz, C*H*OSi), 2.02-2.15 (2H, m, CHCH_2CCH); 1.88 (1H, t, *J* 2.6 Hz, $CHCH_2CCH$); 1.63-1.37 (2H, m, CH_2); 1.33-1.10 (13H, m, CH_2); 0.81 0.83 (9H, s, OSi(CH_3)$_3$); 0.81 (3H, t, *J* 6.6 Hz, CH_3); -0.01 (6H, dd, *J* 4.5 Hz, OSi(CH_3)$_2$)

δ_C (75.5 MHz; $CDCl_3$); 81.8, 70.9, 69.7, 36.6, 31.8, 29.6, 29.2, 27.3, 25.8, 25.1, 22.6, 18.0, 14.0, -4.4, -4.6.

HRMS (ESI^+) *calcd* for $C_{17}H_{34}NaOSi$ [M+Na^+] *m/z* 282.5368 found: *m/z* 282.5361.

4.1.6.9: (*E*)-*N*-phenethyltridec-4-enamide (3.84)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and (*E*)-decenyl boronic acid (0.074 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.05 mmol), 1,4-dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *N*-phenethyl-acrylamide (0.04 g, 0.20 mmol) in 1,4-dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 16 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: ethyl acetate 4:1) to give the title product as colourless oils (yield 0.06 g, 93%).

R_f (petrol: ethyl acetate, 4:1) 0.4;

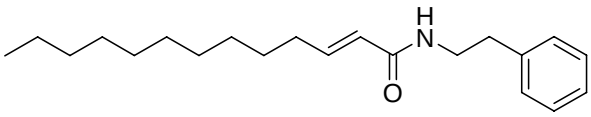
ν_{max} (KBr)/cm^{-1}; 2932 (C=C), 2852 (C=C), 1658, 1527 (C=O amide).

δ_H (300 MHz; $CDCl_3$), 7.36-7.10 (5H, m, Ph); 5.71 (1H, br s, N*H*); 5.60 (1H, dt, *J* 17.0, 1.5 Hz C*H* alkene); 5.47 (1H, dt, *J* 17.0, 1.5 Hz C*H* alkene); 3.50 (2H, q, *J* 6.8 Hz, NHC$H_2$$CH_2$); 2.97 (2H, d, *J* 7.5 Hz, CH_2CH_2CO); 2.80 (2H, q, *J* 6.8 Hz, NHCH$_2$CH_2); 1.96 (2H, q, *J* 7.5 Hz, CH_2CH$_2$CO); 1.36-1.19 (14H, m, CH_2); 0.88 (3H, t, *J* 6.8 Hz, CH_3).

δ_C (75.5 MHz; $CDCl_3$); 170.7, 135.4, 128.7, 128.7, 128.5, 126.4, 121.4, 40.5, 35.5, 35.2, 31.8, 29.5, 29.4, 29.2, 29.1, 27.1, 22.6, 22.6, 14.0.

HRMS (ESI^+) *calcd* for $C_{21}H_{33}N_1Na_1O_1$ [M+Na^+] *m/z* 338.2460 found: *m/z* 338.2448.

4.1.6.10: (*E*)-N-phenethyltridec-2-enamide (3.85)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol), potassium (trans-1-dec-1-enyl)trifluoroborane (0.099 g, 0.40 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.009 g, 0.017 mmol). 1,4-Dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *N*-phenethyl-acrylamide (0.04 g, 0.20 mmol) in 1,4-dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 16 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: ethyl acetate 4:1) to give the title product as colourless oils (yield 0.056 g, 89%).

R_f (petrol: ethyl acetate, 4:1) 0.4;

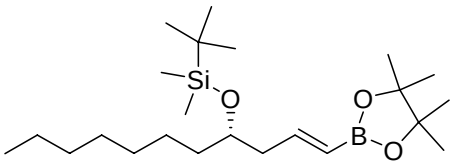
ν_{max} (KBr)/cm^{-1}; 3279 (N-H), 3028,2934 (C=C), 1657, 1625 (C=O);

δ_H (300 MHz; $CDCl_3$), 7.36-7.16 (5H, m, Ph); 5.95 (1H, dt, *J* 12.0, 7.5 Hz C*H* alkene); 5.53 (1H, dt, *J* 12.0, 1.5 Hz C*H* alkene); 5.42 (1H, br s, N*H*); 3.50 (2H, q, *J* 6.8 Hz, NHC$H_2$$CH_2$); 2.78 (2H, t, *J* 6.8 Hz, $NHCH_2CH_2$); 2.53 (2H, q, *J* 7.2 Hz, CH_2CHCHCO); 1.40-1.11 (16H, m, CH_2); 0.81 (3H, t, *J* 6.6 Hz, CH_3).

δ_C (75.5 MHz; $CDCl_3$); 166.5, 145.7, 138.9, 128.7, 128.6, 126.4, 122.0, 40.2, 35.6, 31.8, 29.5, 29.4, 29.3, 29.3, 28.7, 22.6, 14.0.

HRMS (ESI^+) *calcd* for $C_{21}H_{33}N_1Na_1O_1$ [M+Na^+] *m/z* 338.2460 found: *m/z* 338.2444.

4.1.6.11: (*S,E*)-tert-butyldimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-1-en-4-yloxy)silane (3.86)



Tert-butyl-dimethyl-((S)-1-prop-2-ynyl-octyloxy)-silane (2.05 g, 5.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.71 g, 5.5 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added sequentially bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.13 g, 0.5 mmol) followed by triethylamine (0.05 g, 0.5 mmol) the mixture was capped then heated at 60 ºC for 16 hours protected from light. Upon completion hexane (5 mL) was added and mixture stirred for 10 minutes. The material was isolated through a short silica pad (elution: hexanes) to give the title product as a colourless oil (yield 1.91 g, 93%)

R_f (petrol: diethyl ether, 40:1) 0.3;

$[\alpha]_D^{20}$ = -12.8 º (*c* = 0.105, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2929 (C=C), 2856 (C=C), 1638 (C-O), 1361 (B-O), 1094, 909 (O-Si)

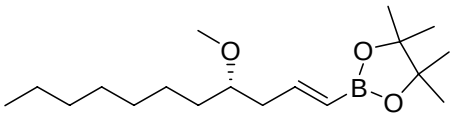
δ_H (300 MHz; $CDCl_3$), 6.59 (1H, dt, *J* 18.0, 7.0 Hz C*H* alkene); 5.31 (1H, dt, *J* 18.0, 1.5 Hz C*H* alkene); 3.71 (1H, quint, *J* 6.0 Hz, C*H*$OSiR_3$), 2.35-2.24 (2H, m, CHCH_2CHCH); 1.48-1.34 (2H, m, CH_2); 1.31-1.16 (20H, m, CH_2, CH_3); 0.83 (9H, s, OSi(CH_3)$_3$); 0.81 (3H, t, *J* 6.6 Hz, CH_3); 0.03 (6H, s, OSi(CH_3)$_2$).

δ_C (75.5 MHz; $CDCl_3$); 151.7, 83.3, 72.2, 44.6, 37.5, 32.2, 30.0, 29.6, 26.3, 26.2, 25.7, 25.1, 23.0, 14.4, -3.9, -4.1, C-B peak not observed.

δ_B (96.3 MHz; $CDCl_3$); 28.7 Hz

HRMS (ESI^+) *calcd* for $C_{23}H_{47}B_1Na_1O_3Si_1$ [M+Na^+] *m/z* 433.3285 found: *m/z* 433.3272.

4.1.6.12: 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (3.94)



(*S*)-4-Methoxy-undec-1-yne (4.56 g, 25.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.36 g, 26.3 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added sequentially bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.65 g, 2.50 mmol) followed by triethylamine (0.25 g, 2.50 mmol) the mixture was capped then heated at 60 ºC for 16 hours protected from light. Upon completion hexane (5 mL) was added and mixture stirred for 10 minutes. The material was isolated through a short silica pad (elution: hexanes) to give the title product as a colourless oil (yield 7.06 g, 91%)

R_f (petrol: diethyl ether, 20:1) 0.3;

$[\alpha]_D^{20}$ = -8.9 º (*c*=0.95, $CHCl_3$);

ν_{max} (neat)/cm^{-1}; 2980 (C=C), 2932 (C=C), 1714 (C-O), 1358 (B-O).

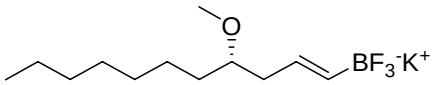
δ_H (300 MHz; $CDCl_3$), 6.57 (1H, dt, *J* 17.0, 7.0 Hz C*H* alkene); 5.42 (1H, dt, *J* 17.0, 1.3 Hz C*H* alkene); 3.26 (3H, s, OCH_3); 3.18 (1H, quint, *J* 5.6 Hz, C*H*OCH_3), 2.56-2.19 (2H, m, CHCH_2CHCH); 1.33-1.26 (2H, m, CH_2); 1.04-1.25 (22H, m, CH_2); 0.88 (3H, t, *J* 6.6 Hz, CH_3).

δ_C (75.5 MHz; $CDCl_3$); 151.0, 83.4, 80.5, 56.8, 40.3, 34.0, 32.2, 30.1, 29.7, 25.7, 25.17, 25.15, 24.9, 23.0, 14.5. C-B peak not observed.

δ_B (96.3 MHz; $CDCl_3$); 31.1 Hz

HRMS (ESI^+) *calcd* for $C_{18}H_{35}B_1NaO_3$ [M+Na^+] *m/z* 333.2577 found: *m/z* 333.2589.

4.1.6.13: Potassium 2-((E)-(S)-4-Methoxy-undec-1-enyl)-trifluoroborate (3.99)



2-((*E)-(S)*-4-Methoxy-undec-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1.55 g, 5.0 mmol) in acetonitrile (10 mL), was charged to a 25 mL round bottom flask under an atmosphere of nitrogen. The flask was cooled to 0 ºC (ice/salt) and to the resulting solution was added sequentially potassium hydrogen difluoride (1.56 g, 20 mmol) followed by water (4 mL). The mixture was capped, warmed to room temperature and stirred for 3 hours until a heavy white precipitate forms. Upon completion the reaction mixture is concentrated in *vacuo* and thoroughly dried under high vacuum (0.01 mmHg). The solids were then washed with copious acetone (250 mL) and filtered to remove inorganic salts. The solvent was concentrated to approximately 20 mL and diethyl ether (100 mL) was added and the flask triturated to precipitate the product. Storage overnight in a -20 ºC freezer gave the product as a white solid (yield 0.55 g, 38%).

Mp (Acetone) = 170 ºC (dec.)

$[\alpha]_D^{20}$ = -8.4 º (*c* = 0.65, MeOH);

ν_{max} (KBr)/cm^{-1}; 2929 (C=C), 2856 (C=C), 1652 (C-O), 1378, 1299 1103, 970 (B-F).

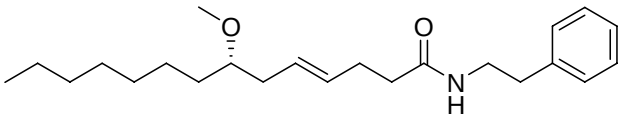
δ_H (300 MHz; CD_3OD), 6.81 (1H, dt, *J* 18.0, 6.8 Hz, C*H* alkene); 6.48 (1H, dt, *J* 18.0, 3.8 Hz, C*H* alkene); 4.35 (3H, s, OCH_3); 4.24 (1H, quint, *J* 5.8 Hz, C*H*OCH_3), 1.98 (2H, ddd, *J* 18.0, 6.8, 1.5 Hz, CHCH_2CHCH); 2.62-2.40 (2H, m, CH_2); 2.40-2.22 (10H, m, CH_2); 1.92 (3H, t, *J* 6.6 Hz, CH_3).

δ_C (75.5 MHz; CD_3OD); 133.8, 82.9, 82.8, 56.6, 40.8, 34.5, 33.0, 30.9, 30.5, 26.4, 23.7, 14.4, C-B peak not observed.

δ_B (96.3 MHz; CD_3OD); -4.2 Hz

HRMS (ESI^+) *calcd* for $C_{14}H_{24}B_1F_3O_1$ [$M+H^+$] *m/z* 251.1794 found: *m/z* 251.1784.

4.1.6.14: Hermitamide A (3.67)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.012 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *N*-phenethyl-acrylamide (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 24 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: ethyl acetate 4:1) to give the title product as light yellow oils (yield 0.052 g, 72%).

R_f (petrol: ethyl acetate, 4:1) 0.2;

$[\alpha]_D^{20}$ = -9.1 º (*c*=1.05, $CHCl_3$); lit = -9.3 º ($CHCl_3$)[11]

ν_{max} (KBr)/cm^{-1}; 3302 (N-H), 2929 (C=C), 2857 (C=C), 1658, 1527 (C=O amide) 1134, 1093.

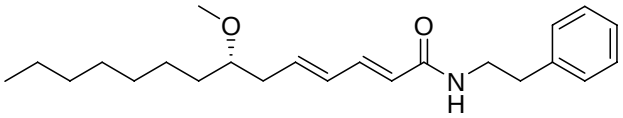
δ_H (500 MHz; C_6D_6), 7.24 (2H, t, *J* 7.3 Hz, Ph); 7.16 (1H, t, *J* 7.3 Hz Ph); 7.10 (2H, d, *J* 7.3 Hz Ph); 5.68 (1H, dt, *J* 15.0, 7.3 Hz C*H* alkene); 5.37 (1H, br s, N*H*); 3.42 (2H, dd, *J* 13.0, 6.6, NHCH_2); 3.21 (3H, s, OCH_3); 3.19-3.15 (1H, m); 2.94 (2H, dd, *J* 13.0, 6.8, Hz, NHCH_2); 2.68 (2H, t, *J* 7.0 Hz, CH_2); 2.20-2.11 (2H, m); 1.63-1.53 (2H, m); 1.52-1.33 (12H, m); 1.01 (3H, t, *J* 7.0 Hz, CH_3).

δ_C (125.8 MHz; $CDCl_3$); 169.7, 139.44, 133.16, 128.9, 128.5, 126.3, 123.1, 79.7, 55.4, 40.7, 35.8, 35.3, 33.3, 32.0, 30.1, 29.6, 28.5, 25.6, 25.4, 23.2, 22.9, 14.1

HRMS (ESI^+) *calcd* for $C_{23}H_{38}N_1O_2$ [$M+H^+$] *m/z* 360.2903 found: *m/z* 360.2897.

All data in accordance with literature values [11]

4.1.6.15: (*S,2E,4E*)-7-methoxy-N-phenethyltetradeca-2,4-dienamide (3.111)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.012 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *N*-phenethyl-acrylamide (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 24 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: ethyl acetate 4:1) to give the title product as light yellow semisolid (yield 0.012 g, 16%).

Mp (petrol) = 32-34 °C

R_f (petrol: ethyl acetate, 4:1) 0.23;

$[\alpha]_D^{20}$ = -8.4 º (*c*=0.70, $CHCl_3$);

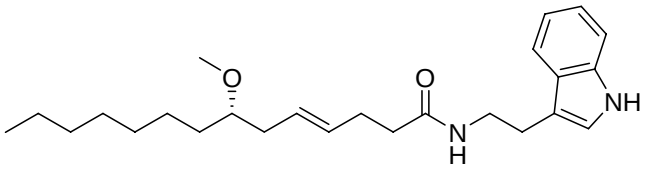
ν_{max} (KBr)/cm^{-1}; 3307 (N-H), 2921 (C=C), 2852 (C=C), 1652, 1525 (C=O Amide) 1128, 1096.

δ_H (500 MHz; C_6D_6), 7.63 (1H, dd, *J* 15.0 7.7 Hz, C*H* alkene); 7.23 (2H, t, *J* 7.3 Hz, Ph); 7.16 (1H, t, *J* 7.3 Hz, Ph); 7.08 (2H, d, *J* 7.3 Hz Ph); 6.20 (1H, dd, *J* 15.0 11.0 Hz, C*H* alkene); 5.96 (1H, dt, *J* 15.0, 7.6 Hz C*H* alkene); 5.43 (1H, d, *J* 15.0 Hz, C*H* alkene); 4.83-4.76 (1H, m, N*H*); 3.48 (2H, dd, *J* 13.0, 6.9 Hz, NHCH_2); 3.21 (3H, s, OCH_3); 3.11 (1H, quint, *J* 6.0 Hz, C*H*OCH_3); 2.62 (2H, t, *J* 7.3, Hz, NHCH_2); 2.68 (2H, t, *J* 7.0 Hz, CH_2); 2.20-2.11 (2H, m, CH_2); 1.61-1.47 (3H, m, CH_2); 1.44-1.32 (10H, m, CH_2); 1.01 (3H, t, *J* 6.8 Hz, CH_3).

δ_C (125.8 MHz; $CDCl_3$); 165.2, 140.7, 139.5, 138.4, 130.5, 128.9, 128.2, 127.6, 122.9, 80.0, 72.2, 70.1, 56.3, 40.8, 37.3, 35.85, 33.9, 32.0, 29.6, 29.5, 25.44, 22.8, 14.1.

HRMS (ESI^+) *calcd* for $C_{23}H_{35}N_1O_2$ [M+H^+] *m/z* 358.2746 found: *m/z* 358.2732.

4.1.6.16: Hermitamide B (3.7)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.012 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *N*-phenethyl-acrylamide (0.04 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 36 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: ethyl acetate 3:1) to give the title product as colourless oils (yield 0.029 g, 36%).

R_f (petrol: ethyl acetate, 3:1) 0.1;

$[\alpha]_D^{20}$ = -5.2 º (*c*=0.55, $CHCl_3$); Lit = -4.9° (c 0.15, $CHCl_3$)[11]

ν_{max} (KBr)/cm^{-1}; 3309 (N-H), 3022, 2930 (C=C), 2852 (C=C), 2849 (C=C) 1658, 1527 (C=O) 976, 911 (CH=CH).

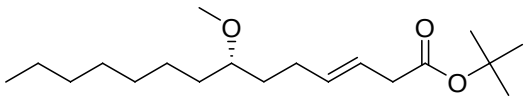
δ_H (300 MHz; $CDCl_3$), 8.24 (1H, br s, N*H*); 7.52 (1H, d, *J* 7.9 Hz, indole); 7.37 (1H, d, *J* 7.9 Hz, indole); 7.20 (1H, td, *J* 7.9, 1.1 Hz, C*H* indole); 7.12 (1H, td, *J* 7.9, 1.1 Hz, C*H* indole); 7.02 (1H, br d, *J* 7.2 Hz C*H* indole); 5.78 (1H, br s, N*H*); 5.60-5.40 (2H, m, alkene); 3.56 (2H, dd, *J* 13.0, 7.2 Hz, NHCH_2), 3.27 (3H, s, CHOCH_3); 3.13 (1H, quint, *J* 5.7 Hz, C*H*OCH_3); 2.97 (2H, t, *J* 6.8 Hz, NHCH_2); 1.33-1.38 (3H, m, CH_2); 2.23-1.95 (3H, m, CH_2); 1.35-1.20 (10H, m, CH_2); 0.88 (3H, t, *J* 6.6 Hz, CH_3).

δ_C (75.5 MHz; $CDCl_3$); 171.4, 136.1, 130.8, 127.6, 127.1, 122.3, 122.1, 119.7, 118.8, 79.7, 55.4, 40.7, 35.8, 35.3, 33.3, 32.0, 30.1, 29.6, 28.5, 25.6, 25.4, 23.2, 22.9, 14.1

HRMS (ESI$^-$) *calcd* for $C_{25}H_{38}N_2O_2$ [M-H^+] *m/z* 397.2855 found: *m/z* 397.2860.

All data in accordance with literature values [11]

4.1.6.17: (*S,E*)-*tert*-butyl 7-methoxytetradec-3-enoate (3.104)



A 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.003 g, 0.006 mmol) and potassium 2-((*E*)-(*S*)-4-Methoxy-undec-1-enyl)-trifluoroborate (0.116 g, 0.40 mmol). 1,5-cyclooctadiene (0.013 g, 0.012 mmol), barium hydroxide octahydrate (0.120 g, 0.40 mmol), dioxane (2 mL) and water (0.2 mL) were added by sequentially by syringe and the vessel was purged with argon. The red solution was stirred for 15 minutes before the addition of *tert*-butyl acrylate (0.026 g, 0.20 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 16 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: diethyl ether 20:1) to give the title product as colourless oils (yield 0.059 g, 95%).

R_f (petrol: ethyl acetate, 40:1) 0.3;

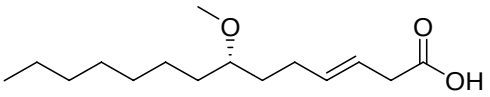
$[\alpha]_D^{20}$ = -8.9 º (*c*=1.1, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}; 2931 (C=C), 2859 (C=C), 1713 (C=O ester), 1370, 1152.

δ_H (500 MHz; C_6D_6), 5.87 (1H, dt, *J* 18.0, 7.3 Hz, C*H* alkene); 5.63 (1H, dt, *J* 18.0, 7.3 Hz, C*H* alkene); 3.26 (3H, s, OCH_3); 3.16-3.01 (3H, m, C*H*CH_2OCH_3), 2.21 (2H, dt, *J* 14.0, 7.3 Hz, CHCHCH_2CO); 1.68-2.48 (4H, m, CH_2); 1.47 (9H, s, OC(CH_3)$_3$); 1.38-1.34 (8H, m, CH_2); 1.01 (3H, t, *J* 6.9 Hz, CH_3).

δ_C (75.5 MHz; $CDCl_3$); 171.7, 133.0, 122.1, 80.8, 80.7, 80.6, 56.8, 34.6, 33.7, 33.5, 32.2, 30.1, 29.7, 25.6, 28.5, 25.6, 23.6, 23.1, 14.5.

4.1.6.18: (*S,E*)-7-Methoxytetradec-3-enoic acid (3.105)



A 10 mL round bottom flask was charged with (*S,E*)-*tert*-butyl 7-methoxytetradec-3-enoate (0.047 g, 0.15 mmol) in dichloromethane (5 mL). To this was added trifluoroacetic acid (0.5 mL) and the reaction stirred at room temperature for 6 hours. Upon completion the crude reaction mixture was concentrated *in vacuo* and azeotroped with dichloromethane (3 x 5 mL). The crude residue was purified by flash column chromatography on silica gel (petrol: diethyl ether 1:1) to give the title product as light yellow oils (yield 0.038 g, 98%).

R_f (petrol: ethyl acetate, 1:1) 0.2;

$[\alpha]_D^{20}$ = -9.1 º (*c*=1.1, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}; 3076 (O-H), 2931 (C=C), 2857 (C=C), 1709 (C=O ester), 1090.

δ_H (500 MHz; C_6D_6), 5.68-5.44 (2H, m, C*H* alkene); 3.31 (3H, s, OCH_3); 3.19-3.12 (3H, m, C*H*CH_2OCH_3), 2.11 (2H, q, *J* 7.3 Hz, CHCHCH_2CO); 1.60-1.46 (2H, m, CH_2); 1.46-1.38 (2H, m, CH_2); 1.36-1.18 (10H, m CH_2); 0.88 (3H, t, *J* 6.8 Hz, CH_3).

δ_C (125.7 MHz; $CDCl_3$); 177.8, 133.5, 120.4, 80.2, 56.11, 37.0, 32.8, 31.6, 31.8, 29.7, 29.0, 25.2, 23.2, 22.6, 14.01.

HRMS (ESI^-) *calcd* for $C_{15}H_{27}O_3$ [$M\text{-}H^+$] *m/z* 255.1960 found: *m/z* 255.1943.

4.2 References

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